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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c)

Docket Number	P-16069	Type a plus sign (+) inside this box -->	+

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TITLE OF THE INVENTION (280 characters max)

SELECTIVE ESTROGEN RECEPTOR MODULATORS

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	A check or money order is enclosed to cover the Provisional filing fees	PROVISIONAL FILING FEE AMOUNT ($)	$160.00
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Respectfully submitted,
SIGNATURE 

Date 01 22 / 04

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REGISTRATION NO. (*if appropriate*) 43,972

X Additional inventors are being named on separately numbered sheets attached hereto

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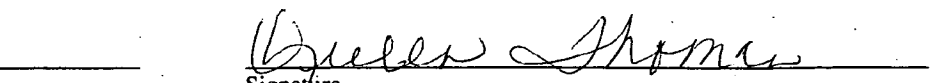
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SELECTIVE ESTROGEN RECEPTOR MODULATORS

Field of Invention

The present invention is in the field of medicine, particularly in the treatment of gynecological disorders. More specifically, the present invention relates to selective estrogen receptor modulators useful to treat endometriosis and uterine fibrosis.

Background of the Invention

Uterine leiomyoma/leiomyomata (uterine fibroid disease) is an old and ever present clinical problem that goes under a variety of names, including uterine fibrosis, uterine hypertrophy, uterine lieomyomata, myometrial hypertrophy, fibrosis uteri, and fibrotic metritis. Essentially, uterine fibrosis is a condition where there is an inappropriate deposition of fibroid tissue on the wall of the uterus. This condition is a cause of dysmenorrhea and infertility in women.

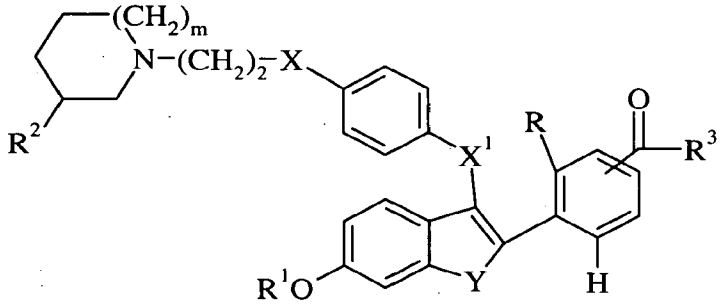
Endometriosis is a condition of severe dysmenorrhea, which is accompanied by severe pain, bleeding into the endometrial masses or peritoneal cavity and often leads to infertility. The symptom's cause appears to be ectopic endometrial growths that respond inappropriately to normal hormonal control and are located in inappropriate tissues. Because of the inappropriate locations for endometrial growth, the tissue seems to initiate local inflammatory-like responses causing macrophage infiltration and a cascade of events leading to initiation of the painful response. Evidence suggests that a cause of uterine fibrosis and endometriosis is an inappropriate response of fibroid tissue and/or endometrial tissue to estrogen.

Many publications have appeared within the last ten years disclosing novel selective estrogen receptor modulators (SERMs), *e.g.*, U.S. Patent No.'s 5,484,795, 5,484,798, 5,510,358, 5,998,401 and WO 96/09040. Many of these SERMs, generally speaking, have been found to have a beneficial estrogen agonist activity in the bone and cardiovascular systems with a concomitant beneficial estrogen antagonist activity in the breast. A small, particularly useful subset of such compounds has also been found to have an estrogen antagonist effect in the uterus. A compound with this particularly useful SERM profile holds particular promise in treating uterine leiomyoma/leiomyomata and/or endometriosis.

However, the actual use of these SERM compounds, particularly in pre-menopausal women, has been hampered due to said compound's stimulatory effect on the ovaries. A great need currently exists, therefore, for new SERM compounds that behave as estrogen antagonists in the uterus that do not stimulate the ovaries.

Summary of Invention

The present invention relates to a compound of formula I:

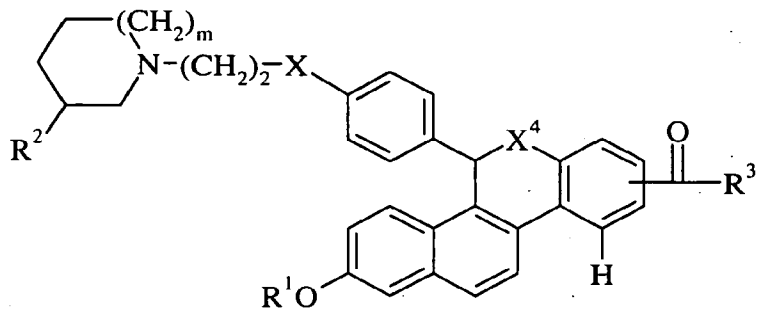


I;

wherein:

m is 0, 1 or 2;

R is H and X^1 is O, CH_2 or CO or R combines with X^1 to form a moiety of the formula:

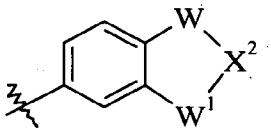


wherein X^4 is O or S;

R^1 is H, SO_2(n-C_4-C_6 alkyl) or COR^4;

R^2 is H or methyl provided that if m is 1 or 2, then R^2 must be H and that if m is 0, then R^2 must be methyl;

R^3 is NR^5R^6 or OR^7 or when R is H, R^3 may combine with the phenyl with which it is attached to form a moiety of the formula:



wherein

W and W^1 are CH_2 or C=O provided that at least one of W or W^1 must be C=O;

X^2 is NR^8 or O;

R^8 is H or C_1-C_6 alkyl;

X is O or NR^9;

Y is S or CH=CH;

R^4 is C_1-C_6 alkyl, C_1-C_6 alkoxy, $NR^{10}R^{11}$, phenoxy, or phenyl optionally substituted with halo;

R^5, R^6, R^7 and R^9 are independently H or C_1-C_6 alkyl; and

R^{10} and R^{11} are independently H, C_1-C_6 alkyl or phenyl; or a pharmaceutical salt thereof.

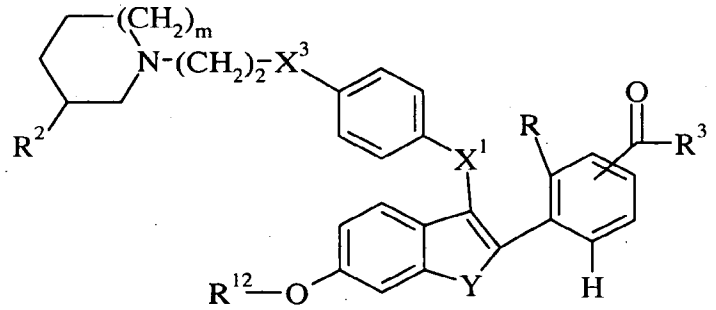
The present invention also relates to a pharmaceutical composition containing a compound of formula I and a pharmaceutical carrier. In another embodiment, the

pharmaceutical composition of the present invention may be adapted for use in treating endometriosis and/or uterine fibrosis.

The present invention also relates to methods for treating endometriosis and/or uterine fibrosis employing a compound of formula I.

In addition, the present invention relates to a compound of formula I for use in treating endometriosis and/or uterine fibrosis. The present invention is further related to the use of a compound of formula I for the manufacture of a medicament for treating endometriosis and/or uterine fibrosis.

The present invention further relates to a compound of formula II:

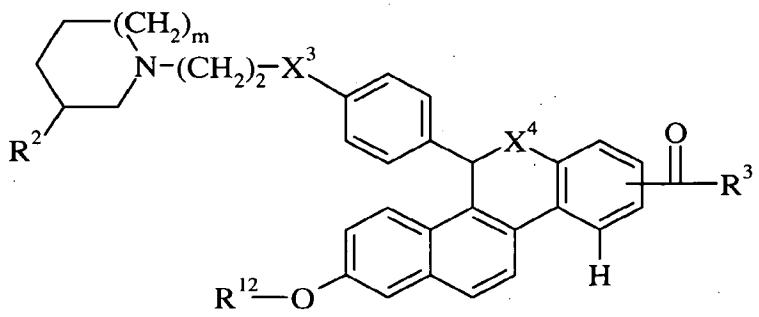


II;

wherein:

m is 0, 1 or 2;

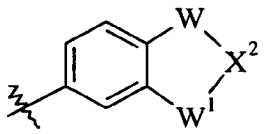
X^1 is O, CH_2 or CO and R is H or R combines with X^1 to form a moiety of the formula:



wherein X^4 is O or S;

R^2 is H or methyl provided that if m is 1 or 2, then R^2 must be H and that if m is 0, then R^2 must be methyl;

R^3 is NR^5R^6 or OR^7 or when R is H, R^3 may combine with the phenyl with which it is attached to form a moiety of the formula:



wherein

W and W^1 are CH_2 or C=O provided that at least one of W or W^1 must be C=O;

X^2 is NR^8 or O;

R^8 is H or C_1-C_6 alkyl;

R^{12} is H, C_1-C_6 alkyl, benzyl, SO_2CH_3, SO_2(n-C_4-C_6 alkyl) or COR^4;

Y is S or CH=CH;

X^3 is O or NR^{13};

R^4 is C_1-C_6 alkyl, C_1-C_6 alkoxy, $NR^{10}R^{11}$, phenoxy, or phenyl optionally substituted with halo;

R^5, R^6 and R^7 are independently H or C_1-C_6 alkyl; and

R^{10} and R^{11} are independently H, C_1-C_6 alkyl or phenyl;

R^{13} is H, C_1-C_6 alkyl or CO_2(C_1-C_6 alkyl); provided that if R^{12} is H, SO_2(n-C_4-C_6 alkyl) or COR^4, then X^3 is NR^{13} and R^{13} is CO_2(C_1-C_6 alkyl); or a salt thereof; useful as an intermediate to a compound of formula I.

Detailed Description

Unless specified otherwise, reference hereafter to a "compound of formula I" includes the pharmaceutical salts thereof. Since the compound of formula I may contain an acidic proton, *i.e.*, when R^3 is OR^7 and R^7 is H, the pharmaceutical salts of the present invention include base addition and acid addition salts thereof.

The compounds of the present invention have one or more chiral centers and may exist in a variety of stereoisomeric configurations. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of

enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All such racemates, enantiomers, and diastereomers are within the scope of the present invention.

For the purposes of the present invention, as disclosed and claimed herein, the following terms are defined below.

The term "halo" refers to fluoro, chloro, bromo and iodo. The term "C_1-C_6 alkyl" represents a straight, branched or cyclic hydrocarbon moiety having from one to six carbon atoms, *e.g.*, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, cyclobutyl, pentyl, cyclopentyl, hexyl, cyclohexyl and the like. Moieties such as a cyclobutylmethylene are also included within the scope of a C_1-C_6 alkyl group. The term "C_1-C_4 alkyl" refers specifically to methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl and cyclobutyl. The term "n- C_4-C_6 alkyl" refers specifically to n-butyl, n-pentyl and n-hexyl. A "C_1-C_6 alkoxy" group is a C_1-C_6 alkyl moiety connected through an oxy linkage.

The term "pharmaceutical" when used herein as an adjective means substantially non-deleterious.

A pharmaceutical "acid addition" salt is a salt formed by reaction of the free base form of a compound of formula I with a pharmaceutical acid, such as described in the Encyclopedia of Pharmaceutical Technology, editors James Swarbrick and James C. Boylan, Vol 13, 1996 "Preservation of Pharmaceutical Products to Salt Forms of Drugs and Absorption". Specific salt forms include, but are not limited to the: acetate, benzoate, benzenesulfonate, 4-chlorobenzenesulfonate; citrate; ethanesulfonate; fumarate; d-gluconate; d-glucuronate; glutarate; glycolate; hippurate; hydrochloride; 2-hydroxyethanesulfonate; dl-lactate; maleate; d-malate; l-malate; malonate; d-mandelate; l-mandelate; methanesulfonate; 1,5 napthalenedisulfonate; 2-naphthalenesulfonate; phosphate; salicylate; succinate; sulfate; d-tartrate; l-tartrate; and p-toluenesulfonate.

A pharmaceutical "base addition" salt is a salt formed by reaction of the free base form of a compound of formula I with a pharmaceutical base, such as described in the Encyclopedia of Pharmaceutical Technology, editors James Swarbrick and James C. Boylan, Vol 13, 1996 "Preservation of Pharmaceutical Products to Salt Forms of Drugs and Absorption". Specific salt forms include, but are not limited to the: calcium,

diethanolamine, diethylamine, ethylenediamine, lysine, magnesium, piperazine, potassium, sodium and tromethamine (Tris, Trizma) salts.

The term "patient" as used herein refers to female humans and non-human female animals such as companion animals (dogs, cats, horses and the like).

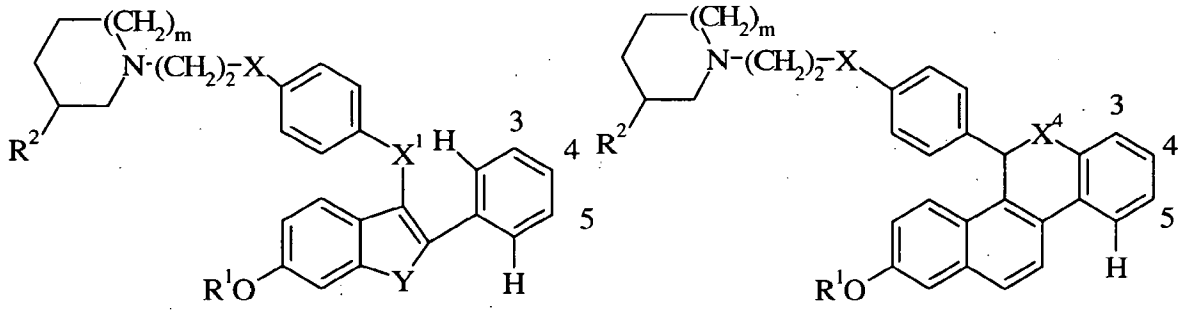
The terms "treating" and "treat" as used herein means alleviating, ameliorating, preventing, prohibiting, restraining, slowing, stopping, or reversing the progression or severity of a pathological condition, or sequela thereof, described herein. The term "preventing" means reducing the likelihood that the recipient of a compound of formula I will incur, further incur or develop any of the pathological conditions, or sequela thereof, described herein.

The term "a patient in need thereof" is a patient either suffering from the caimed pathological condition or sequela thereof or is a patient at a recognized risk thereof as determined by medical diagnosis, *i.e.*, as determined by the attending physician.

As used herein, the term "effective amount" means an amount of a compound of formula I that is capable of treating the conditions described herein.

Preferred Compounds and Embodiments of the Invention

Certain compounds of the invention are particularly interesting and are preferred. The following listing sets out several groups of preferred compounds. It will be understood that each of the listings may be combined with other listings to create additional groups of preferred compounds. The following numbering system will be used to describe the preferred positions of the COR^3 moiety:

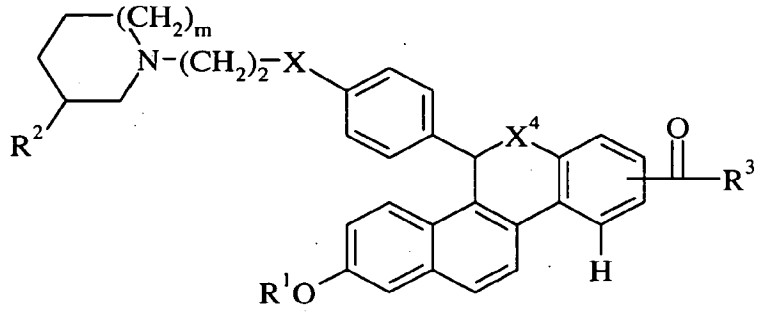


a) m is 1 or 2;

b) m is 1;

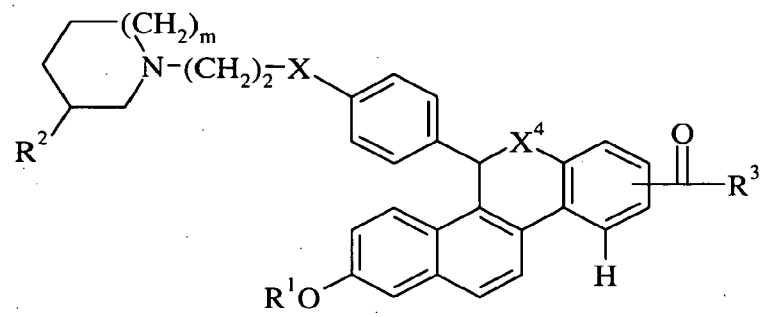
c) R is H;

d) R combines with X^1 to form a moiety of the formula:



;

e) R combines with X^1 to form a moiety of the formula:



and X^4 is O;

f) R^1 is H;

g) R^1 is H or COR^4 and R^4 is C_1-C_6 alkyl, $NHCH_3$ or phenyl;

h) R^1 is H or COR^4 and R^4 is C_1-C_4 alkyl, $NHCH_3$ or phenyl;

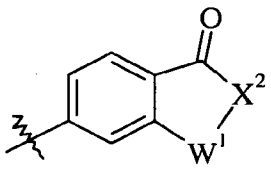
i) R^3 is NR^5R^6 and R^5 and R^6 are independently H or C_1-C_4 alkyl;

j) R^3 is OR^7 and R^7 is H or C_1-C_4 alkyl;

k) the $C(O)R^3$ moiety is at position 3 or 4;

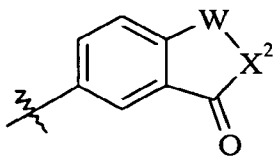
l) the $C(O)R^3$ moiety is at position 4;

m) R is H and R^3 combines with the phenyl with which it is attached to form:



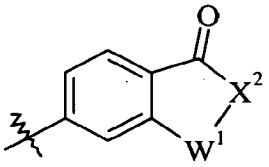
and W^1 is CH_2 and X^2 is NR^8 and R^8 is H;

n) R is H and R^3 combines with the phenyl with which it is attached to form:



and R^8 is H or C_1-C_4 alkyl;

o) R is H and R^3 combines with the phenyl with which it is attached to form:



and R^8 is H or C_1-C_4 alkyl;

p) X is O;

q) X is NR^9 and R^9 is H or methyl;

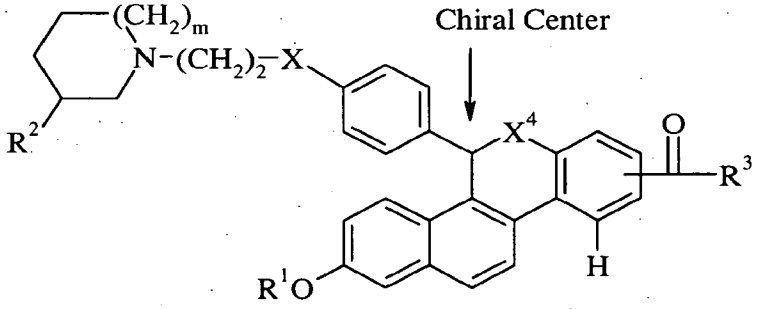
r) X^1 is O or CH_2;

s) X^1 is O;

t) Y is CH=CH;

u) the hydrochloride salt form.

With respect to the chiral center designated below:



an enantiomeric excess (ee) of greater than 90% is preferred, an ee of greater than 95% is most preferred and an ee of greater than 99% is most especially preferred. Enantiomeric enrichment is readily determined by one of ordinary skill in the art using standard techniques and procedures, such as gas or high performance liquid chromatography with a chiral column (see, e.g., J. Jacques, et al., "Enantiomers, Racemates, and Resolutions",

John Wiley and Sons, Inc., 1981; E.L. Eliel and S.H. Wilen," Stereochemistry of Organic Compounds", (Wiley-Interscience 1994), and European Patent Application No. EP-A-838448, published April 29, 1998). Of course, the preferred enantiomer is that which possesses favorable activity in the biological assays disclosed herein. In order to verify the identify of the preferred enantiomer in any given racemic mixture, the activity of the individual isomers should be verified in the biological assays described herein.

The preferred patient of treatment is a female human.

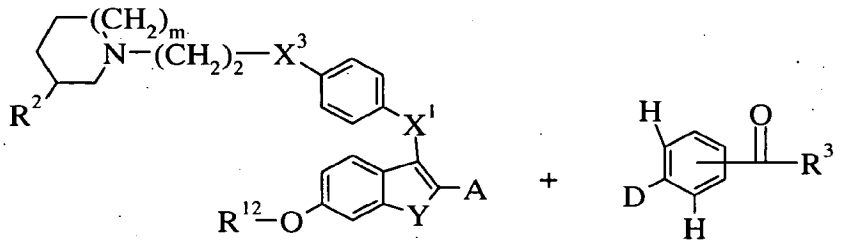
The compound of formula I is preferably formulated in a dosage unit form, *i.e.*, in an individual delivery vehicle, for example, a tablet or capsule, prior to administration to the recipient woman.

The compound of formula I is preferably administered orally.

Synthesis

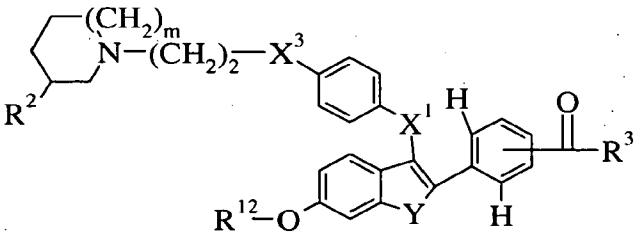
The compound of formula I may be prepared as described in the following Schemes and Examples.

Scheme 1



III

IV

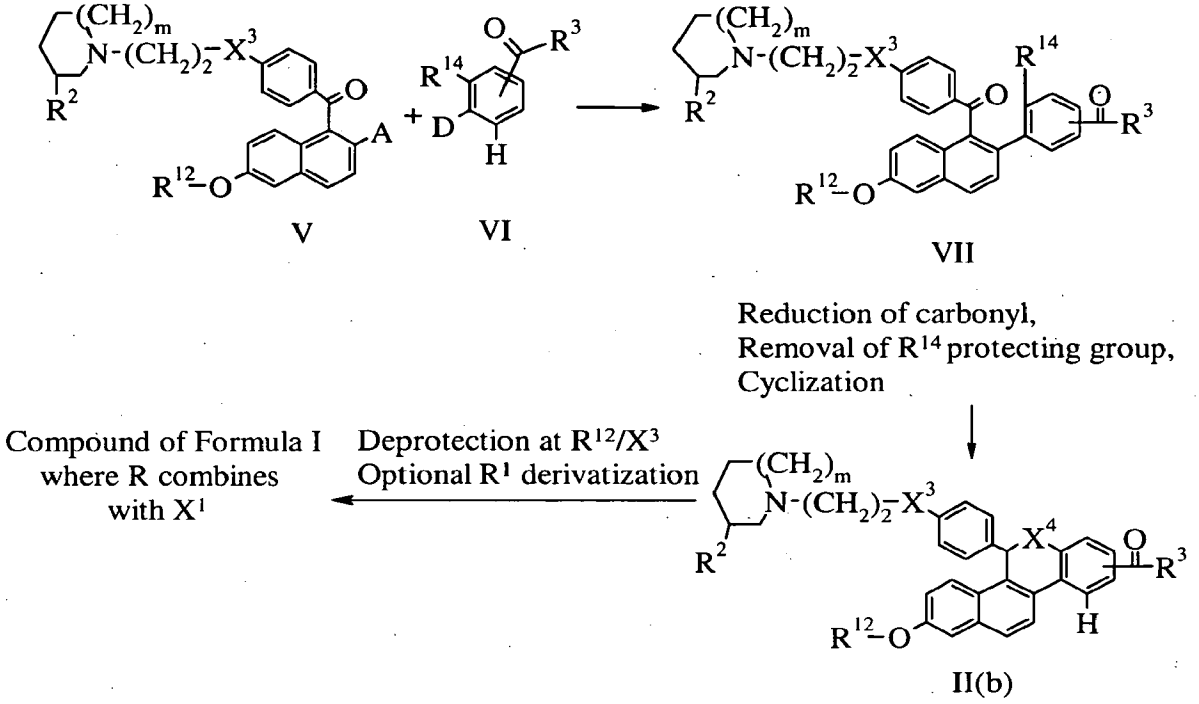


II

Deprotection of R^{12}/X^3 if needed and
Optional R^1 derivatization

Compound of Formula I
where R is H

Scheme 2



In Scheme 1, a compound of formula IV is reacted with a compound of formula III under usual "Suzuki" or "Stille" reaction conditions, *i.e.*, wherein one of substituent "A" or "D" is a boronic acid/ester or alkyl stannane moiety and the other is a leaving group, *e.g.*, chloro, bromo or iodo or a sulfonate group such as trifluoromethyl sulfonate to give the corresponding compound of formula I or II(a).

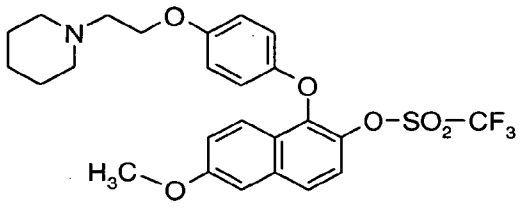
In Scheme 2, where R^{14} is fluoro or alkyl or benzyl protected thio or hydroxy, a compound of formula V is reacted with a compound of formula VI under usual "Suzuki" or "Stille" reaction conditions as described above to form a compound of formula VII. When R^{14} is protected hydroxy, said hydroxy group is typically removed in order to promote the following reduction/cyclization reaction. Said protecting group may be removed via standard procedure, e.g., those described in the latest edition of Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, N.Y. (Greene). After removal of the hydroxy protecting group (when present), the keto group found in the resulting product compound of formula VII may then be reduced under standard conditions, e.g., employing borane to provide the corresponding alcohol. This reduced product may then be cyclized under standard conditions, e.g., when R^{14} is F, base

catalyzation with potassium t-butoxide or when R^{14} is other than F, acid catalyzation with HCl, to provide the corresponding compound of formula I or II(b).

When R^{12} is SO_2CH_3, C_1-C_6 alkyl or benzyl (preferably methyl, benzyl or SO_2CH_3) said hydroxy protecting groups may be removed under standard conditions (see, *e.g.*, the procedures that follow or Greene) to provide the compound of formula I where R^1 is H. Similarly, when X^3 is NR^{13} and R^{13} is $CO_2(C_1$-C_6 alkyl), said amino protecting group may also be removed as taught in Greene. A formula I compound where R^1 is H may be further derivatized employing standard acylation or sulfonylation methodology to prepare a compound of formula I where R^1 is COR^4 or $SO_2(n$-C_4-C_6 alkyl).

Preparation 1

Trifluoromethanesulfonic acid 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester



Add 6-methoxynaphthalene-2-ol (20 g, 114.8 mmol) to dimethylformamide (DMF, 250 mL) at ambient temperature followed by *N*-bromosuccinimide (NBS, 21.5 g, 120 mmol) over a 30 minute period. After 45 minutes, dilute with water (800 mL), collect and dry the precipitate to provide 25.5 g (87%) of 1-bromo-6-methoxy-naphthalen-2-ol.

Add 1-bromo-6-methoxy-naphthalen-2-ol (66.7 g, 264 mmol), potassium carbonate (K_2CO_3, 40.0 g, 290 mmol) and benzyl bromide (49.6 g, 290 mmol) to DMF (800 mL). Stir the mixture at ambient temperature for 1 hour. Add water (400 mL) to precipitate the product. Collect the precipitate and wash the filter cake with heptane (3 X 125 mL) then dry to provide 83.7 g of 2-benzyloxy-1-bromo-6-methoxy-naphthalene (86.2%).

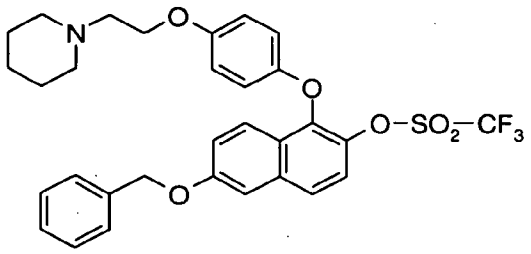
Combine toluene (200 mL), 2-benzyloxy-1-bromo-6-methoxy-naphthalene (30 g, 87.4 mmol), 4-(2-piperidin-1-yl-ethoxy)phenol (23.2 g, 105 mmol) and cesium carbonate (34.4 g, 105 mmol), and heat the mixture to reflux. Remove a portion of the toluene (100 mL). Add ethyl acetate (390 mg, 4.37 mmol) and copper triflate benzene complex (2.20 g, 4.37 mmol) to the reaction mixture and stir for 5 minutes. Remove the solvent by distillation and heat the resulting residue to 174°C for 1.5 hours. Dissolve the residue in a mixture of ethyl acetate (200 mL) and aqueous HCl (1 N, 90 mL). Separate and concentrate the organics to a residue. Column chromatograph the residue to give 12.4 g of 1-{2-[4-(2-benzyloxy-6-methoxy-naphthalen-1-yloxy)-phenoxy]-ethyl}-piperidine (30%).

Add 1-{2-[4-(2-benzyloxy-6-methoxy-naphthalen-1-yloxy)-phenoxy]-ethyl}-piperidine (12.4 g, 25.5 mmol) to a methanol/ethyl acetate mixture (1:1, 490 mL) and heat to form a solution. Remove the heat and add ammonium formate (4.83 g, 76.6 mmol) and $Pd(OH)_2$ on carbon (20 % ww, 1.58 g, 1.12 mmol). Reflux for 50 minutes then filter the mixture. Concentrate the filtrate to provide 9.9 g of 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalene-2-ol (98.5%).

Cool dichloromethane (290 mL), triethylamine (3.08 g, 30.4 mmol) and 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalene-2-ol (9.2 g, 23.4 g) to -50°C and add trifluoromethane sulfonic acid anhydride (7.26 g, 25.7 mmol). Stir the resulting mixture at -50°C for 2 hours then allow the mixture to warm to ambient temperature before stirring for an additional hour. Add brine (150 mL) and separate the organics. Wash the organics with $NaHCO_3$ then dry before concentrating to a residue. Crystallize the residue with ethyl ether – hexanes to provide 11.2 g of the title compound (90.9%).

Preparation 2

Trifluoromethanesulfonic acid 6-benzyloxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester

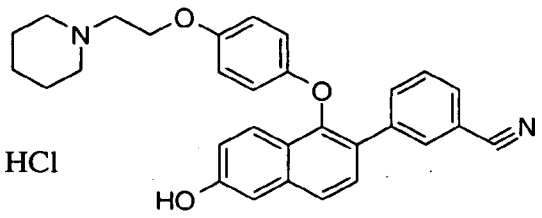


Add 2M hydrogen chloride in ether (1.5 mL, 3 mmol) to a solution of trifluoromethanesulfonic acid 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester (1.07 g, 2.04 mmol) in dichloromethane (20 mL) and remove solvent under vacuum. Dissolve the hydrochloride salt in dichloromethane (40 mL) and cool in ice bath. Add boron tribromide (0.58 mL, 6.12 mmol), stir 3.5 hours, warm to ambient temperature and stir for 15 minutes, cool in ice bath and quench with ice cold saturated aqueous sodium bicarbonate. Extract aqueous layer with dichloromethane, combine organic layers and dry with magnesium sulfate, remove solvent under vacuum and chromatograph on silica gel using dichloromethane/methanol mixtures to give 99 mg (95%) of trifluoromethanesulfonic acid 6-hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester. Mass spectrum (ion spray): m/z= 512 (M+1).

Combine trifluoromethanesulfonic acid 6-hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester (247 mg, 0.48 mmol), triphenylphosphine (190 mg, 0.725 mmol), benzyl alcohol (0.075 mL, 0.725 mmol) and tetrahydrofuran (5 mL) in an ice bath. Add diisopropyl azodicarboxylate (0.14 mL, 0.725 mmol), stir 1 hour, warm to ambient temperature and stir 30 minutes. Dilute with ethyl acetate and wash with 50% saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dry with magnesium sulfate and remove solvent under vacuum. Chromatograph on silica gel with dichloromethane/methanol mixtures to give 213 mg (73%) of the title compound: Mass spectrum (ion spray): m/z=602 (M+1).

Preparation 3

3-{6-Hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-benzonitrile hydrochloride

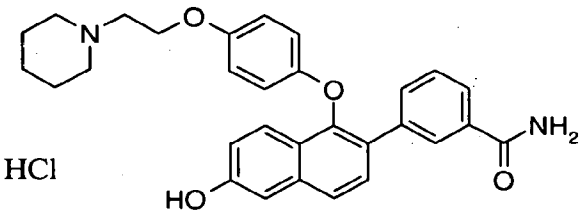


Combine trifluoromethanesulfonic acid 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester (740 mg, 1.41 mmol), 3-cyanobenzeneboronic acid (620 mg, 4.23 mmol), palladium(II)acetate (31.6 mg, 0.14 mmol), tricyclohexylphosphine (59.3 mg, 0.21 mmol), cesium fluoride (1.93 g, 12.68 mmol) and acetonitrile (15 mL) and heat at 90°C. After 10 minutes, cool to ambient temperature, filter and remove solvent under vacuum. Dissolve in dichloromethane and filter through Celite. Chromatograph on silica gel with dichloromethane/methanol mixtures and add 1M hydrogen chloride in ether (1.5 mL) to give 730 mg (100%) of 3-{6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-benzonitrile hydrochloride.

Dissolve 3-{6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-benzonitrile hydrochloride (730 mg, 1.411 mmol) in dichloromethane (20 mL), cool in an ice bath and add 1M boron tribromide in dichloromethane (4.23 mL, 4.23 mmol). Let slowly warm to ambient temperature over 18 hours, quench with saturated sodium bicarbonate, dry organic layer with magnesium sulfate, filter and chromatograph on silica gel with dichloromethane/methanol mixtures. Combine fractions containing product, add 1M hydrogen chloride in ether (1.5 mL) and remove solvent under vacuum to give 670 mg (98%) of the title compound. Mass spectrum (ion spray): m/z= 465.2 (M+1).

Example 1

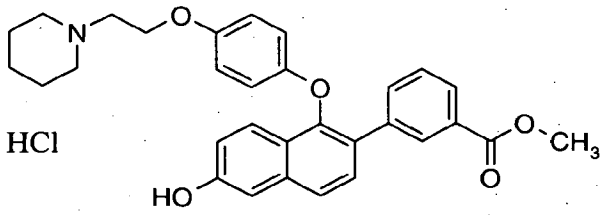
3-{6-Hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-benzamide hydrochloride



Heat a solution of 3-{6-hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-benzonitrile hydrochloride (68 mg, 0.14 mmol) in concentrated hydrochloric acid (8 mL) at 70°C for 2 hours, cool to ambient temperature and remove the solvent under reduced pressure. Dissolve in 5% methanol/dichloromethane and wash with saturated sodium bicarbonate, saturated sodium chloride, dry with magnesium sulfate, filter and chromatograph on silica gel with dichloromethane/methanol mixtures. Combine fractions containing product and add 1M hydrogen chloride in ether (0.5 mL). Remove the solvent under reduced pressure to give 62 mg (88%) of the title compound. Mass spectrum (ion spray): m/z= 483.3 (M+1).

Example 2

3-{6-Hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-benzoic acid methyl ester hydrochloride

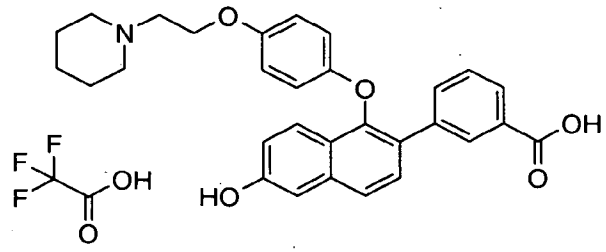


Heat a suspension of 3-{6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-benzonitrile hydrochloride (190 mg, 0.37 mmol) in concentrated hydrochloric acid (5 mL) in a sealed vessel at 130°C for 3.5 hours, then cool to ambient temperature and remove the solvent under reduced pressure. Coevaporate with methanol (3X). Redissolve in methanol and add 4M hydrogen chloride in dioxane (1 mL). Reflux

for 1 hour, then cool to ambient temperature and evaporate under reduced pressure. Dissolve in 5% methanol/dichloromethane and wash with saturated sodium bicarbonate, dry with magnesium sulfate and chromatograph on silica gel with dichloromethane/methanol mixtures. Combine fractions containing product and add 1M hydrogen chloride in ether (0.25 mL) and remove the solvent under reduced pressure to give 140 mg (73%) of the title compound.

Example 3

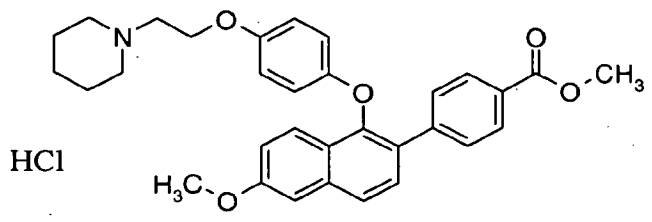
3-{6-Hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-benzoic acid trifluoroacetate



Heat a suspension of 3-{6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-benzonitrile hydrochloride (100 mg, 0.20 mmol) in concentrated hydrochloric acid (5 mL) in a sealed vessel at 130°C for 3.5 hours, then cool to ambient temperature and remove the solvent under reduced pressure. Chromatograph on reversed phase C-18 silica gel with water/acetonitrile/trifluoroacetic acid mixtures. Combine fractions containing product and remove the solvent under reduced pressure to give 44 mg (37%) of the title compound. Mass spectrum (ion spray): m/z= 484.1 (M+1).

Example 4

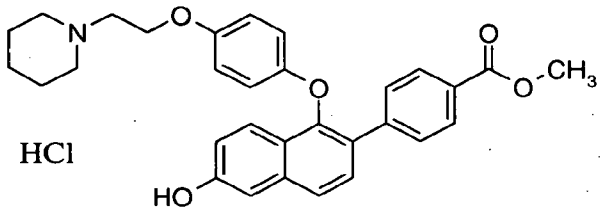
4-{6-Methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-benzoic acid methyl ester hydrochloride



Using a method similar to that described for the preparation of 3-{6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-benzonitrile hydrochloride, obtain 254 mg (79%) of the title compound using [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II)complex with dichloromethane (1:1) (480 mg, 1.0 equivalent) as catalyst system and 4-methoxycarbonylphenyl boronic acid. Mass spectrum (ion spray): m/z=512 (M+1).

Example 5

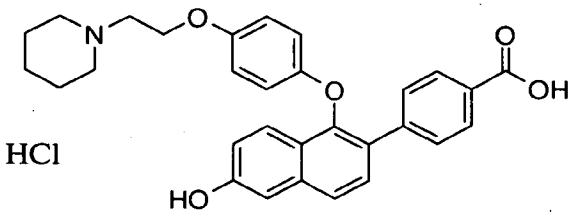
4-{6-Hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-benzoic acid methyl ester hydrochloride



Using a method similar to that described for the preparation of 3-{6-hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-benzonitrile hydrochloride, convert 4-{6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-benzoic acid methyl ester hydrochloride to 49 mg (25%) of the title compound. Mass spectrum (ion spray): m/z= 498 (M+1).

Example 6

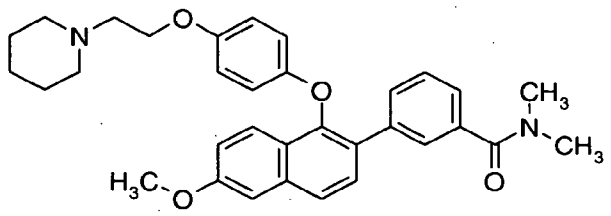
4-{6-Hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-benzoic acid hydrochloride



Add 1N aqueous sodium hydroxide solution (0.15 mL) to a solution of 4-{6-hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-benzoic acid methyl ester hydrochloride (35 mg, 0.071 mmol) in tetrahydrofuran (1 mL), stir and heat at 60°C. After 3 hours, cool to ambient temperature and remove solvent under a stream of nitrogen. Chromatograph on reversed phase silica gel with dilute aqueous hydrochloric acid/acetonitrile mixtures to give 4.8 mg (13%) of the title compound. Mass spectrum (ion spray): m/z= 484 (M+1).

Example 7

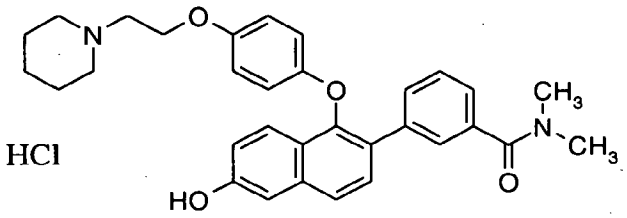
3-{6-Methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-N,N-dimethyl-benzamide



Combine N,N-dimethylbenzamide-3-boronic acid (300 mg, 1.55 mmoL), trifluoro-methanesulfonic acid 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester (273 mg, 0.52 mmoL), cesium fluoride (710 mg, 4.68 mmoL) and acetonitrile (5 mL) in a 50 mL flame-dried flask fitted with a reflux condenser. In a separate flask combine palladium(II) acetate (11 mg, 0.05 mmoL) and tricyclohexylphosphine (21 mg, 0.075 mmoL). Add acetonitrile (2.5 mL) and sonicate for 10 minutes under nitrogen. Add the catalyst slurry to the mixture of substrates and heat in a 90°C oil bath for 40 minutes. Cool the suspension to room temperature and filter through GF/F filter paper. Rinse the filter cake with acetonitrile and concentrate the filtrate in vacuo. Partition the residue between ethyl acetate (25 mL) and 5% aqueous sodium carbonate (25 mL). Separate and wash the organic layer with saturated aqueous NH_4Cl, and saturated aqueous NaCl. Dry the organic layer (Na_2SO_4), filter, and evaporate to obtain 440 mg of crude material. Chromatograph the residue on a SiO_2 column eluting the material with 2.5% methanol in dichloromethane to give 258 mg (94%) of the title compound: mass spectrum (ion spray): m/z = 525.4 (M+H).

Example 8

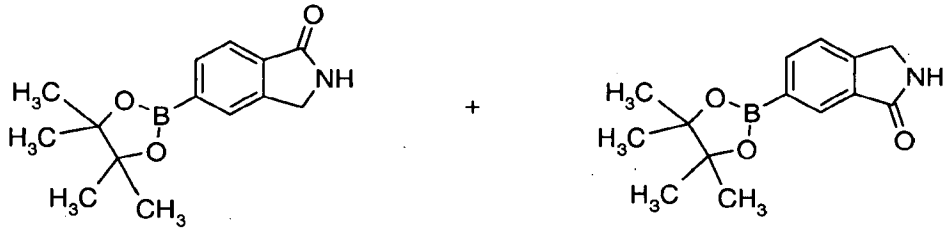
3-{6-Hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-N,N-dimethyl-benzamide, hydrochloride salt



Dissolve 3-{6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-N,N-dimethyl-benzamide in ethyl acetate (10 mL) and diethyl ether (5 mL). Add 2M HCl in diethyl ether (250 µL, 500 µmol). Concentrate the slurry and dry in vacuo. Dilute the residue in dichloromethane (10 mL) and blanket with nitrogen. Cool the solution to 3°C with external ice bath and treat with BBr_3 (250 µL, 2.65 mmoL). After 2 hours, dilute the reaction mixture with ethyl acetate (40 mL), methanol (5 mL), and saturated aqueous $NaHCO_3$ (20 mL). Separate the layers and back extract the aqueous layer with ethyl acetate (10 mL). Combine the organic layers and wash with a 1:1 solution of water and brine (10 mL). Dry with Na_2SO_4, filter, and concentrate in vacuo. Chromatograph the residue (264 mg) on a SiO_2 column eluting the material with methanol in dichloromethane (2.5 to 10%). Dissolve the free base in diethyl ether (5.0 mL), ethyl acetate (6.0 mL) and methanol (1.0 mL) and add 2M HCl in diethyl ether. Collect the precipitate on filter paper, rinse with diethyl ether and dry in vacuo (<2mm of Hg) at 65°C for 48 hours to give 175 mg (65%) of the title compound: mass spectrum (ion spray): m/z = 511.3 (M+1).

Preparation 4

Mixture of 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-2,3-dihydro-isoindol-1-one and 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2,3-dihydro-isoindol-1-one



To a stirring room temperature solution of 4-bromophthalimide (3.00 g, 13.27 mmol) in ethanol (10 mL) and tetrahydrofuran (65 mL), under a blanket of nitrogen, add sodium borohydride (1.97 g, 53.10 mmol) in portions. Stir this mixture at ambient temperature for 8 hours and then quench with 2N HCl (12 mL) and then excess water. Extract the resulting aqueous mixture with diethyl ether then ethyl acetate. Wash the combined extracts with water and brine; dry (sodium sulfate) and concentrate them *in vacuo*. Recrystallize the resulting solid in CH_2Cl_2 to give a mixture of 5-bromo-3-hydroxy-2,3-dihydro-isoindol-1-one and 6-bromo-3-hydroxy-2,3-dihydro-isoindol-1-one, 2.21 g. Concentrate the mother liquor *in vacuo* and purify the resulting material on a flash column (silica gel; 0%-5% MeOH gradient in CH_2Cl_2) to provide an additional 450 mg of product.

To a stirring room temperature solution of the mixture of 5-bromo-3-hydroxy-2,3-dihydro-isoindol-1-one and 6-bromo-3-hydroxy-2,3-dihydro-isoindol-1-one 9 (2.00 g, 8.77 mmol) in trifluoroacetic acid (30 mL) add triethylsilane (1.82 mL, 11.40 mmol) in portions, via syringe. Stir this mixture at ambient temperature for 2-3 hours and then quench over saturated aqueous sodium bicarbonate. Extract the resulting aqueous mixture with ethyl acetate. Wash the combined extracts with saturated aqueous sodium bicarbonate, water and brine; dry (sodium sulfate) and concentrate them *in vacuo*. Purify the resulting material on a flash column (silica gel; 20% THF/hexanes with a bit of CH_2Cl_2 added when loading material on column) to provide 1.72 g (93%) of a mixture of 5-bromo-2,3-dihydro-isoindol-1-one and 6-bromo-2,3-dihydro-isoindol-1-one.

Place the mixture of 5-bromo-2,3-dihydro-isoindol-1-one and 6-bromo-2,3-dihydro-isoindol-1-one (770 mg, 3.63 mmol), bis(pinacolato)diboron (1.38 g, 5.45 mmol),

$PdCl_2(dppf)_2 \cdot CH_2Cl_2$ (93 mg, 0.127 mmol), potassium acetate (1.07 g, 10.90 mmol) and anhydrous dimethyl sulfoxide (10 mL) in a round bottom flask. Put the reaction in an oil bath and stir it at 90°C for 15 hours. Cool the reaction to ambient temperature, quench with ample water and extract the resulting aqueous mixture with dichloromethane. Wash the combined extracts with water and brine; then dry (sodium sulfate) and evaporate them *in vacuo* to give the title compounds as a mixture of two components, 960 g (>95%).

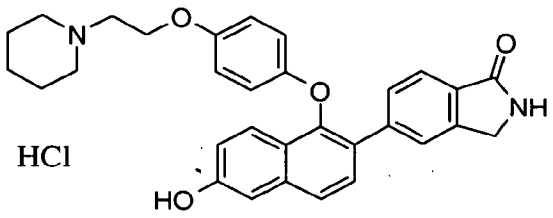
Examples 9 and 10

Mixture of 5-{6-Benzyloxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-2,3-dihydro-isoindol-1-one and 6-{6-Benzyloxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-2,3-dihydro-isoindol-1-one

In a round bottom flask add trifluoromethanesulfonic acid 6-benzyloxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester (600 mg, 0.94 mmol), the mixture of Preparation 4 (929 mg, 3.57 mmol), a sonicated suspension of palladium(II) acetate (43 mg, 0.192 mmol) and tricyclohexylphosphine (79 mg, 0.282 mmol) in acetonitrile (4 mL), and cesium fluoride (1.29 g, 8.46 mmol). Add acetonitrile (25 mL) and immediately place the reaction in a preheated oil bath at 90°C, and stir for 8 hours. Then cool the reaction to ambient temperature and filter it through a pad of Celite (rinse with ample, hot ethyl acetate). Wash the filtrate with 50% aqueous sodium carbonate, saturated aqueous ammonium chloride, water and brine; then dry (sodium sulfate) and evaporate it *in vacuo*. Purify the resulting residue on a flash column (silica gel; 3%-8% MeOH gradient in CH_2Cl_2). Split into two portions and purify on a chromatotron (silica gel; 3% TEA/32% hexanes/65% EtOAc gradient to 3% TEA/20% hexanes/77% EtOAc) to obtain 142 mg (26%) of 5-{6-benzyloxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-2,3-dihydro-isoindol-1-one: MS (IS+) *m/e* 586 $(M + H)^+$ and 20 mg (4%) of 6-{6-benzyloxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-2,3-dihydro-isoindol-1-one. MS (IS+) *m/e* 586 $(M + 1)^+$.

Example 11

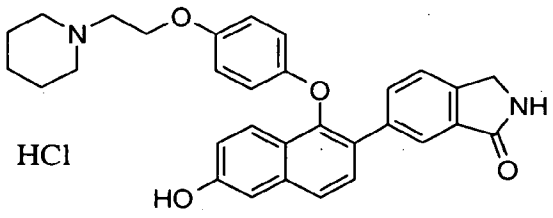
5-{6-Hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-2,3-dihydro-isoindol-1-one hydrochloride salt



To a round bottom flask add 5-{6-benzyloxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-2,3-dihydro-isoindol-1-one (131 mg, 0.224 mmol), ammonium formate (106 mg, 1.67 mmol), 10% Pd/C (0.021 g, ~15% by weight) and MeOH (7 mL). Heat the mixture at reflux for 30 minutes. Cool the reaction to ambient temperature and filter it through a pad of Celite, then rinse the Celite with ample hot methanol. Evaporate the filtrate *in vacuo* and purify the resulting residue by radial chromatography over silica (5%-12% MeOH gradient in CH_2Cl_2) to provide the product free base, 77 mg. Dissolve the purified material in MeOH (5 mL) and add 0.32 mL (2 eq) of a 1.0M solution of hydrochloric acid in diethyl ether. Shake this solution for 5 minutes at ambient temperature and evaporate it *in vacuo* to provide the title compound, 81 mg (68%). MS (IS+) *m/e* 496 $(M + H - HCl)^+$.

Example 12

6-{6-Hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-2,3-dihydro-isoindol-1-one hydrochloride salt



To a round bottom flask add 6-{6-benzyloxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-2,3-dihydro-isoindol-1-one (16 mg, 0.027 mmol), ammonium formate (13 mg, 0.21 mmol), 10% Pd/C (0.010 g) and MeOH (5 mL). Heat the mixture at

reflux for 30 minutes. Cool the reaction to ambient temperature and filter it through a pad of Celite, then rinse the Celite with ample hot methanol. Evaporate the filtrate *in vacuo* and purify the resulting residue by radial chromatography over silica (5%-12% MeOH gradient in CH_2Cl_2) to provide the product free base, 8 mg. Dissolve the purified material in MeOH (2 mL) and add 0.07 mL (2 eq) of a 1.0M solution of hydrochloric acid in diethyl ether. Shake this solution for 1-2 minutes at ambient temperature and evaporate it *in vacuo* to provide the title compound, 9 mg (63%). MS (IS+) *m/e* 496 $(M + H - HCl)^+$.

Preparation 5

Mixture of 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3H-isobenzofuran-1-one and 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3H-isobenzofuran-1-one

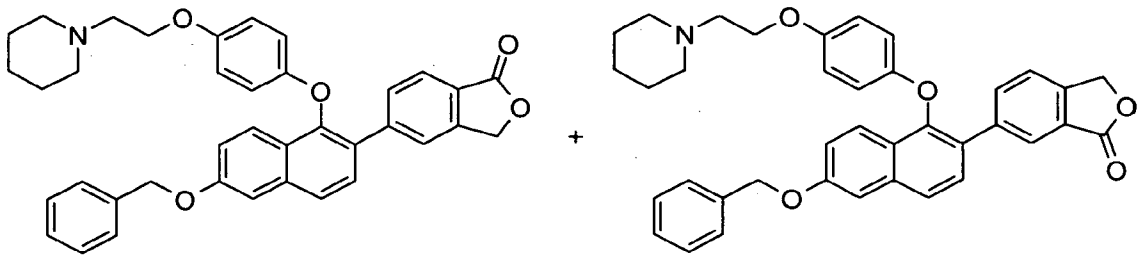
To a stirring room temperature solution of 4-bromophthalic anhydride (3.00 g, 13.22 mmol) in ethanol (10 mL) and tetrahydrofuran (50 mL), under a blanket of nitrogen, add sodium borohydride (1.96 g, 52.86 mmol), in portions. Stir this mixture at ambient temperature for 8 hours and then quench with 2N HCl (12 mL) and then excess water. Extract the resulting aqueous mixture with diethyl ether then ethyl acetate. Wash the combined extracts with water and brine; dry (sodium sulfate) and concentrate them *in vacuo* to give a mixture of 5-bromo-3H-isobenzofuran-1-one and 6-bromo-3H-isobenzofuran-1-one, 2.78 g (98%). Use as is without purification.

Place the mixture of 5-bromo-3H-isobenzofuran-1-one and 6-bromo-3H-isobenzofuran-1-one (1.50 g, 7.04 mmol), bis(pinacolato)diboron (2.06 g, 8.10 mmol), $PdCl_2(dppf)_2 \cdot CH_2Cl_2$ (180 mg, 0.246 mmol), potassium acetate (2.07 g, 21.13 mmol) and anhydrous dimethyl sulfoxide (22 mL) in a round bottom flask. Put the reaction in an oil bath and stir it at 85°C for 8 hours. Cool the dark brown colored reaction to ambient temperature, quench with ample water and extract the resulting aqueous mixture with dichloromethane. Wash the combined extracts with water and brine; then dry (sodium

sulfate) and evaporate them *in vacuo*. Purify the resulting dark solid on a flash column (silica gel; 0%-20% gradient of THF in CH_2Cl_2 then 5% MeOH/20% THF/CH_2Cl_2) to provide the product as a mixture of the two title components, 785 mg (43%).

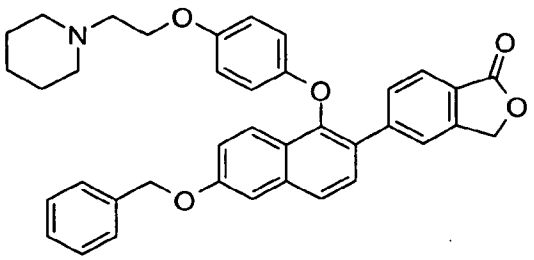
Example 13

Mixture of 5-{6-Benzyloxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-3H-isobenzofuran-1-one and 6-{6-Benzyloxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-3H-isobenzofuran-1-one



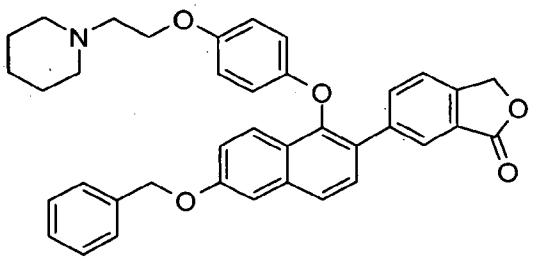
In a round bottom flask add trifluoromethanesulfonic acid 6-benzyloxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester) (592 mg, 0.984 mmol), the mixture of 5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3H-isobenzofuran-1-one and 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3H-isobenzofuran-1-one (0.640 g, 2.46 mmol), a sonicated suspension of Palladium(II) Acetate (0.049 g, 0.220 mmol) and Tricyclohexylphosphine (0.091 g, 0.320 mmol) in acetonitrile (4 mL), and cesium fluoride (1.35 g, 8.86 mmol). Add acetonitrile (25 mL) and immediately place the reaction in a preheated oil bath at 90°C, and stir for 25 minutes. Then cool the reaction to ambient temperature and filter it through a pad of Celite (rinse with ample, hot ethyl acetate). Wash the filtrate with 50% aqueous sodium carbonate, saturated aqueous ammonium chloride, water and brine; then dry (sodium sulfate) and evaporate it *in vacuo*. Purify the resulting brown solid foam on a flash column (silica gel; 4%-10% MeOH gradient in CH_2Cl_2).

Example 14



The mixture of Example 13 was split into three portions and each purified on a Chromatotron (silica gel; 4%-10% MeOH gradient in EtOAc) to obtain the title compound, 0.121 g (21%): MS (IS+) *m/e* 586 $(M + H)^+$.

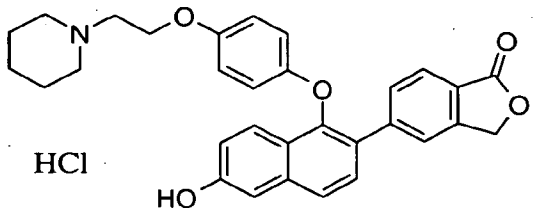
Example 15



The mixture of Example 13 was split into three portions and each purified on a Chromatotron (silica gel; 4%-10% MeOH gradient in EtOAc) to obtain the title compound, 0.185 g (32%): MS (IS+) *m/e* 586 $(M + H)^+$.

Example 16

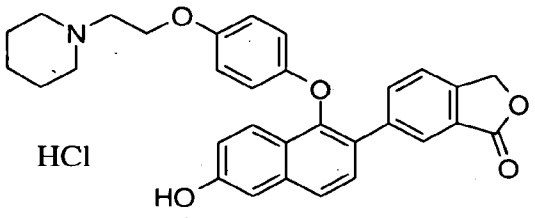
5-{6-Hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-3H-isobenzofuran-1-one hydrochloride salt



To a round bottom flask add the product from Example 14 (0.111 g, 0.190 mmol), ammonium formate (0.090 g, 1.42 mmol), 10% Pd/C (0.017 g, ~15% by weight) and MeOH (12 mL). Heat the mixture at reflux for 30 minutes. Cool the reaction to ambient temperature and filter it through a pad of Celite, then rinse the Celite with ample hot methanol. Evaporate the filtrate *in vacuo* and purify the resulting residue by radial chromatography over silica (5%-10% MeOH gradient in CH_2Cl_2) to provide the product free base, 62 mg. Dissolve the purified material in CH_2Cl_2 (1.5 mL) and MeOH (1.5 mL) and add 0.252 mL (2 eq) of a 1.0M solution of hydrochloric acid in diethyl ether. Shake this solution for 1 minute at ambient temperature and evaporate it *in vacuo* to provide the title compound, 67 mg (66%). MS (IS+) *m/e* 496 $(M + H - HCl)^+$.

Example 17

6-{6-Hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-3H-isobenzofuran-1-one hydrochloride salt



To a round bottom flask add the product from Example 15 (0.156 g, 0.267 mmol), ammonium formate (0.126 g, 2.00 mmol), 10% Pd/C (0.024 g, ~15% by weight) and MeOH (12 mL). Heat the mixture at reflux for 30 minutes. Cool the reaction to ambient temperature and filter it through a pad of Celite, then rinse the Celite with ample hot methanol. Evaporate the filtrate *in vacuo* and purify the resulting residue by radial chromatography over silica (5%-10% MeOH gradient in CH_2Cl_2) to provide the product free base, 73 mg. Dissolve the purified material in CH_2Cl_2 (1.5 mL) and MeOH (1.5 mL) and add 0.300 mL (2 eq) of a 1.0M solution of hydrochloric acid in diethyl ether. Shake this solution for 1 minute at ambient temperature and evaporate it *in vacuo* to provide the title compound, 79 mg (56%). MS (IS+) *m/e* 496 $(M + H - HCl)^+$.

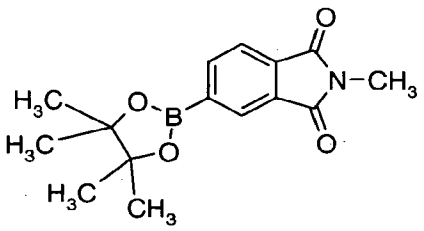
Preparation 6

5-Bromo-2-methyl-isoindole-1,3-dione

To a stirring room temperature solution of 4-bromophthalimide (1.02 g, 4.51 mmol) in dimethylformamide (20 mL) add 60% sodium hydride (0.235 g, 5.87 mmol). Stir this mixture at ambient temperature for 15 minutes and then add iodomethane (0.628 mL, 10.09 mmol). Stir the reaction for 30 minutes at ambient temperature then quench it with brine. Extract the resulting aqueous mixture with ethyl acetate. Wash the combined extracts with brine; dry (sodium sulfate) and concentrate them *in vacuo*. Purify the resulting material on a flash column (silica gel; 70%-100% CH_2Cl_2 gradient in hexanes) to obtain the title compound, 0.960 g (89%). MS (IS+) *m/e* 240 (M + H, ^{79}Br), 242 (M + H, ^{81}Br).

Preparation 7

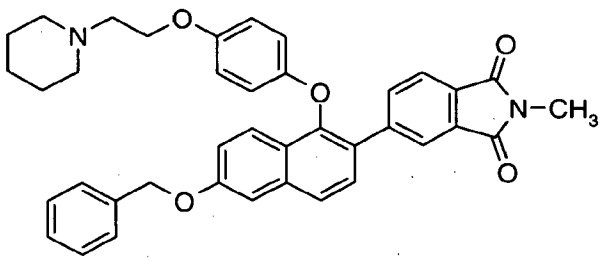
2-Methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-isoindole-1,3-dione



Place 5-bromo-2-methyl-isoindole-1,3-dio 6 (0.920 g, 3.83 mmol), Bis(pinacolato)diboron (1.07 g, 4.21 mmol), $PdCl_2(dppf)_2 \cdot CH_2Cl_2$ (0.098 g, 0.134 mmol), potassium acetate (1.13 g, 11.49 mmol) and anhydrous dimethyl sulfoxide (12 mL) in a round bottom flask. Put the reaction in an oil bath and stir it at 85°C for 8 hours. Cool the dark brown colored reaction to ambient temperature, quench with ample water and extract the resulting aqueous mixture with dichloromethane. Wash the combined extracts with water and brine; then dry (sodium sulfate) and evaporate them *in vacuo*. Purify the resulting dark solid on a flash column (silica gel; 2%-15% gradient of EtOAc in CH_2Cl_2) to provide the title compound, 0.67 g (61%). MS (IS-) *m/e* 204 (M - H – pinacol ester)$^-$, (IS+) *m/e* 288 $(M + H)^+$.

Example 18

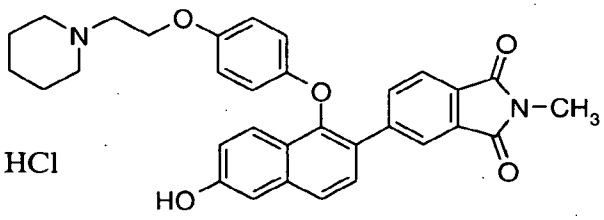
5-{6-Benzyloxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-2-methyl-isoindole-1,3-dione



In a round bottom flask add trifluoromethanesulfonic acid 6-benzyloxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester (0.200 g, 0.332 mmol), 2-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-isoindole-1,3-dione (0.239 g, 0.831 mmol), Palladium(II) Acetate (0.015 g, 0.066 mmol) and tricyclohexylphosphine (0.028 g, 0.099 mmol). Add cesium fluoride (0.454 g, 2.99 mmol) and immediately add acetonitrile (12 mL). Place the reaction in a preheated oil bath at 90°C, and stir for 25 minutes. Then cool the reaction to ambient temperature and filter it through a pad of Celite (rinse with ample, hot ethyl acetate). Wash the filtrate with 50% aqueous sodium carbonate, saturated aqueous ammonium chloride, water and brine; then dry (sodium sulfate) and evaporate it *in vacuo*. Purify the resulting tan solid on a Chromatotron (silica gel; 2%-8% MeOH gradient in CH_2Cl_2) to obtain the title compound, 0.154 g (76%). MS (IS+) *m/e* 613 $(M + H)^+$.

Example 19

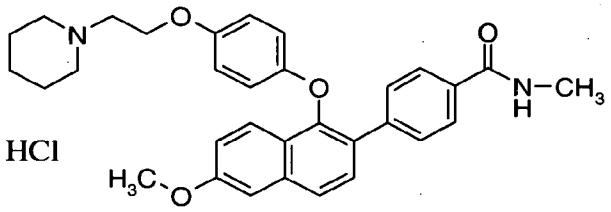
5-{6-Hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-2-methyl-isoindole-1,3-dione hydrochloride salt



To a round bottom flask add the product from Example 18 (0.136 g, 0.222 mmol), ammonium formate (0.105 g, 1.67 mmol), 10% Pd/C (0.020 g, ~15% by weight) and MeOH (7.5 mL). Heat the mixture at reflux for 30 minutes. Cool the reaction to ambient temperature and filter it through a pad of Celite, then rinse the Celite with ample hot methanol. Evaporate the filtrate *in vacuo* and purify the resulting residue by radial chromatography over silica (5%-12% MeOH gradient in CH_2Cl_2) to provide the product free base, 75 mg. Dissolve the purified material in CH_2Cl_2 (2 mL) and MeOH (2 mL) and add 0.287 mL (2 eq) of a 1.0M solution of hydrochloric acid in diethyl ether. Shake this solution for 1-2 minutes at ambient temperature and evaporate it *in vacuo* to provide the title compound, 80 mg (64%). MS (IS+) *m/e* 523 $(M + H - HCl)^+$.

Example 20

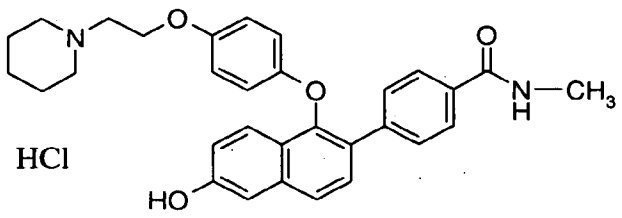
4-{6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-N-methyl-benzamide hydrochloride



Combine trifluoromethanesulfonic acid 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester (200 mg, 0.38 mmol), N-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (300 mg, 1.14 mmol), [1,1'-bis(diphenylphosphino)-ferrocene)dichloropalladium (II), complex with dichloromethane (1:1) (300 mg, 0.38 mmol), cesium fluoride (500 mg, 3.43 mmol) and acetonitrile (4 mL), stir and heat at 85°C. After 18h, cool to ambient temperature and filter through celite. The crude reaction mixture is purified using radial chromatography eluting with 6% methanol in dichloromethane, combining product fractions to 100mg (34%) of a brown oil. The hydrochloride salt is formed by adding 0.8mL of a 1N HCl in Et_2O solution and dried to give 110mg of a tan solid which was used without further purification. Mass spectrum (ion spray): m/z =511(M+1).

Example 21

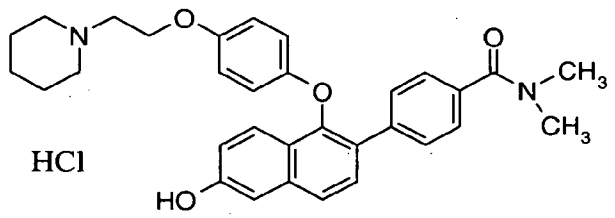
4-{6-hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-N-methyl-benzamide hydrochloride



Charge a 100 mL round-bottom flask with 4-{6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-N-methyl-benzamide hydrochloride (110mg, 0.20mmol) and cool to 0°C under nitrogen. Add 0.6mL of a 1M CH_2Cl_2 solution of BBr_3 and monitor the reaction by ES-MS. After stirring for 1hour, add an additional 0.6mL of a 1M CH_2Cl_2 solution of BBr_3. After stirring an additional hour, pour the reaction into a cold saturated solution of aqueous sodium bicarbonate and ethyl acetate (150mL). Dry the organic layer is dried over sodium sulfate and concentrate *in vacuo*. The crude product is purified by radial chromatography to yield 62 mg (62%) of the free base of the title compound. Form the hydrochloride salt by adding 0.8 mL of a 1N HCl in Et_2O solution to give 73 mg of the title compound. Mass spectrum (ion spray): m/z =497(M+1). HRMS calcd for $C_{31}H_{33}N_2O_4$ (M+H): 497.2440. Found 497.2444.

Example 22

4-{6-Hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-N,N-dimethyl-benzamide hydrochloride



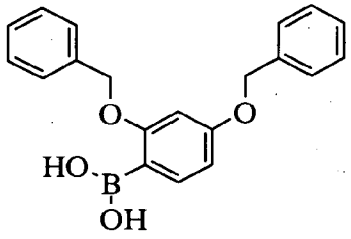
Combine trifluoromethanesulfonic acid 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl ester (247 mg, 0.47 mmol), 4-(N,N-Dimethylaminocarbonyl)phenylboronic acid (272 mg, 1.41 mmol), palladium acetate (II),

(32 mg, 0.14 mmol), cesium fluoride (643 mg, 4.23 mmol), tricyclohexylphosphine (43mg, 0.16 mmol) and acetonitrile (7 mL), stir and heat at 90°C. After 90 min, cool to ambient temperature and filter through celite. Purify the crude reaction mixture using radial chromatography eluting with 4% methanol in dichloromethane, combining product fractions to give 256 mg of 4-{6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-N,N-dimethyl-benzamide. Form the hydrochloride salt by adding 0.8 mL of a 1N HCl in Et_2O solution and dry to give 264 mg of the corresponding hydrochloride salt.

Prepare the title compound in a manner analogous to that of Example 11 using 4-{6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-naphthalen-2-yl}-N,N-dimethyl-benzamide hydrochloride (264mg, 0.47mmol). Purify the crude product by radial chromatography to yield 122 mg (51%) of the free base of title compound. Mass spectrum (ion spray): m/z =511(M+1). Form the hydrochloride salt by adding 0.7 mL of a 1N HCl in Et_2O solution to give 131 mg of the title compound.

Preparation 8

2,4-dibenzyloxyphenyl boronic acid



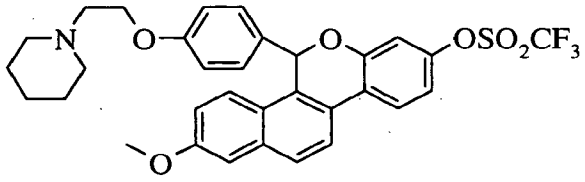
Dissolve 4-bromo-resorcinol 25.0 g (0.132 mol) in 250 mL of DMF. Add K_2CO_3 45.0g (0.31 mol). Add benzylbromide 32.0 mL (0.27 mol) drop wise with vigorous stirring. Heat the reaction to 100 °C until TLC shows no starting phenol (3 to 5 hours). After an aqueous workup, purify the product by flash chromatography on silica gel using 10% ethyl acetate in hexane as eluent. Remove the solvent to give 41.0 g of 4-bromo-resorcinol dibenzyl ether (84%).

Dissolve 4-bromo-resorcinol dibenzyl ether (41.0 g, 0.11 mol) in 200 mL of THF. Add butyllithium (1.6 M in THF) 75.0 mL (0.12 mol) dropwise via syringe at –78 °C with vigorous stirring. Stir the reaction for another hour to ensure complete reaction. Add

triethylborate 20 mL (0.14 mol) all at once. Allow the reaction to warm to room temperature overnight. Pour the reaction mixture into 500 mL of water and 200 mL of ethyl acetate. Separate the layers. Carefully adjust the aqueous phase to pH 7~8 with saturated NH_4Cl and extract with ethyl acetate. Wash the combined organic with brine and dry over $MgSO_4$. Evaporate the solvent to give the title compound.

Preparation 9

Trifluoromethanesulfonic acid 2-methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysen-8-yl ester



Dissolve 2,6-dimethoxynaphthalene 37.6 g (0.20 mol) and 4-(2-(piperidin-1-yl)ethoxy)benzoyl chloride 64.0 g (0.21 mol) in 800 mL of dichloromethane. Add aluminum chloride 133 g (1.00 mol) portionwise and slowly (the first 30 to 50 g must be added slowly to keep the acylation reaction under control so the solvent does not boil off). After all the aluminum chloride has been added, stir the reaction until no more undemethylated compound can be detected either by TLC or HPLC (about 5 hours). Slowly pour the reaction mixture into 1 L of ice/water with vigorous stirring. Decant the top layer water into a separation funnel. Wash the dichloromethane solution and the precipitate with 2N HCl and decant the aqueous layer again into the separation funnel. Extract the aqueous layer with dichloromethane. Adjust the combined dichloromethane solution and the precipitate pH to 8 first with 1N NaOH then with saturated $NaHCO_3$. Filter the mixture. Slurry the solid repeatedly with dichloromethane. Separate the layers of the filtrate and extract the aqueous phase with dichloromethane. Wash the combined organic with brine and dry over $MgSO_4$. Treat the dichloromethane solution with charcoal and filter through a prepackaged "suppelco" silica gel funnel. Evaporate the solvent to give 61.2 g (75.5%) of 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-benzoyl]-naphthalen-2-ol.

Couple 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-benzoyl]-naphthalen-2-ol and 2,4-dibenzyloxyphenyl boronic acid to provide 2-(2,4-dibenzyloxyphenyl)-6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-benzoyl]-naphthalene by the procedure analogous to that described above in Example 18.

Dissolve 10.5 g (20.0 mmol) 2-(2,4-dibenzyloxyphenyl)-6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-benzoyl]-naphthalene in 150 mL of THF. Add LAH 1.5 g (37.0 mmol) portionwise with vigorous stirring at 0 °C. After the addition, allow the reaction to warm up to room temperature and then stir for 3 hours. Cool the reaction in an ice bath and slowly quench with saturated Na_2SO_4. Filter off the solid Al_2O_3 and wash the filter cake with THF (2x50mL). Combine the filtrates, concentrate and purify the residue by flash chromatography on silica gel using CH_2Cl_2 : MeOH (9:1) as eluent to afford 2-methoxy-5-{hydroxy-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methyl}-6-(2,4-benzyloxyphenyl)-naphthalene.

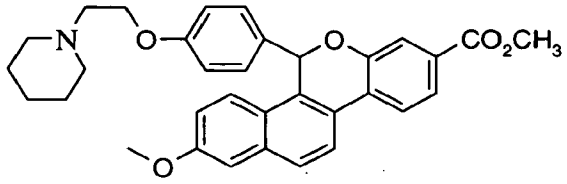
Heat 2-methoxy-5-{hydroxy-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methyl}-6-(2,4-benzyloxyphenyl)-naphthalene to 60°C in THF containg 10% (by weight) of Pd/C (30%) catalyst, overnight under 50 psi of hydrogen atmosphere to afford 2-methoxy-5-{hydroxy-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methyl}-6-(2-hydroxy-4-benzyloxyphenyl)-naphthalene. Treat the THF solution of 2-methoxy-5-{hydroxy-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methyl}-6-(2-hydroxy-4-benzyloxyphenyl)-naphthalene with 10% (by mol) of concentrated HCl to give 1-{2-[4-(8-benzyloxy-2-methoxy-5H-6-oxa-chrysen-5-yl)-phenoxy]-ethyl}-piperidine.

Dissolve 1-{2-[4-(8-benzyloxy-2-methoxy-5H-6-oxa-chrysen-5-yl)-phenoxy]-ethyl}-piperidine (680 mg) in a mixture of 250 ml ethanol and 150 ml THF with warming. Add a slurry of 300 mf 10 % Pd/C in ethanol and react under 1 atmosphere of hydrogen for 18 hours. Filter the catalyst and evaporate the solvent to yield 465 mg of 2-methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysen-8-ol.

Dissolve 2-methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysen-8-ol (118 mg., 0.245 mmoles) in 20 ml methylene chloride and add N-phenyltrifluoromethanesulfonimide (400 mg,. 1.12 mmoles) followed by 1.0 ml of diisopropylethyl amine and stir for 72 hours. Evaporate the solution to a paste and purify by running through an SCX column in methanol (elute with 2N ammonia/methanol) to give 125 mg of the title compound: 125 mg (83%).

Example 23

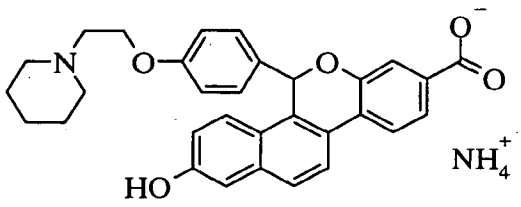
2-Methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-8-carboxylic acid methyl ester



Dissolve trifluoromethanesulfonic acid 2-methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysen-8-yl ester (180 mg.) in 25 ml DMF and add 10 ml of methanol, 0.1 ml triethylamine, palladium acetate (6.7 mg) and 1,1-bis(diphenylphosphino)ferrocene (39.2 mg). Run under carbon monoxide at 1000 psi at 100 degrees for 24 hours. Add Celite and filter, evaporating the solvent to yield a dark oil. Purify on a silica column eluting first with methylene chloride, then with 3% methanol/methylene chloride to elute the product. Evaporate the solvent to yield 52 mg (83%) of the title compound which on LC/MS has a retention time of 3.2 minutes, and a mass of 524 (M+1).

Example 24

2-Hydroxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-8-carboxylic acid ammonium salt

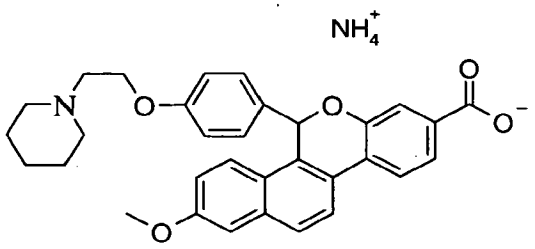


Dissolve 2-methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-8-carboxylic acid methyl ester (20 mg.) in 5.0 ml ethanol and add 1 ml of 5 N sodium hydroxide. Warm on a steam bath for 5 minutes and allow to stand for 2 hours. Remove the solvents under vacuum, and add 20 ml DMF along with sodium t-butyl mercaptan. Seal the vessel, purge with nitrogen and heat at 150 degrees for 24 hours. Remove the

solvent under vacuum, add methanol and acetic acid and run the mixture through an SCX column. Elute the product with 2 N ammonia/methanol. Evaporate the solvent to give 6 mg of the title compound, which on LC/MS has a retention time of 5.2 minutes, and a mass of 496 (M+1).

Example 25

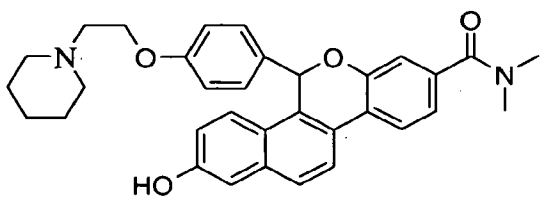
2-Methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-8-carboxylic acid ammonium salt



Dissolve trifluoromethanesulfonic acid 2-methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysen-8-yl ester (23 mg.) in 3 ml of DMSO and add 0.42 mg of palladium II acetate along with 4.2 mg of 1,1-bis(diphenylphosphino)ferrocene and 15 mg of potassium acetate. Seal the vial, purge with carbon monoxide and heat at 60 degrees for 4 hours. At this time add more of the palladium acetate and DPPF, purge with the CO and heat as before. Cool the mixture, add methanol and run through an SCX column, eluting the product with 2 N ammonia/methanol. The product contained both ester and acid, so the ester was hydrolyzed with sodium hydroxide, evaporated to dryness and used in the next step.

Example 26

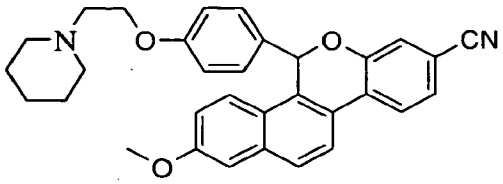
2-Hydroxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-8-carboxylic acid dimethylamide



Dissolve 2-methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-8-carboxylic acid ammonium salt in methylene chloride and add 2 drops of DMF followed by excess oxalyl chloride. After the bubbling stops, evaporate the solvent, add methanol and purify on an SCX column, eluting the product with 2N ammonia/methanol. Deprotect the material with the sodium salt of t-butyl mercaptan in DMF at 110 degrees for 18 hours. Purify using reverse phase chromatography to yield 1.5 mg of the title compound which on LC/MS has a retention time of 2.9 minutes and a mass of 523 (M+1).

Preparation 10

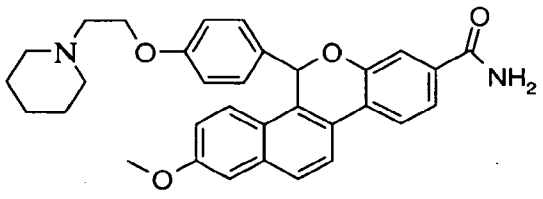
2-Methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-8-carbonitrile



Dissolve trifluoromethanesulfonic acid 2-methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysen-8-yl ester (100 mg., 0.163 mmoles) in 8 ml of DMF and add zinc cyanide (100 mg,. 0.85 mmoles) and palladium (0) tetrakis (triphenylphosphine) (38 mg., 0.033 mmoles). Purge the vial with nitrogen, seal and heat at 80 degrees for 1 hour. Evaporate the DMF, add methanol, filter off and discard the solid, and run the filtrate through an SCX column, eluting the product with 2 N ammonia/methanol. Evaporate the solvent and purify on a small silica column eluting the product with 4% methanol/methylene chloride. Yield 60 mg (75%).

Example 27

2-Methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-8-carboxylic acid amide



Dissolve 2-methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-8-carbonitrile (36 mg.) in 10 ml DMSO and add 85 mg potassium carbonate followed by 100 micoliters of 30% hydrogen peroxide. Stir for 1 hour and add another 100 microliters of hydrogen peroxide and stir for another hour. Filter the reaction, dilute with methanol and pass through an SCX column washing with methanol and eluting the product with 2N ammonia/methanol. Evaporate to dryness to yield 25 mg of the title compound which has a retention time of 5.9 minutes and a mass of 509 (M+1) on LC/MS.

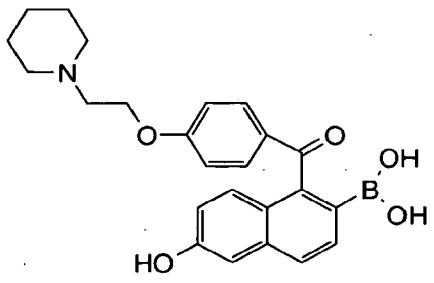
Example 28

2-Hydroxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-8-carboxylic acid amide

Dissolve 2-methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-8-carboxylic acid amide (25 mg.) in 10 ml of DMF and add a large excess of sodium t-butlylthiolate, seal the vial and heat at 110 degrees for 6 hours. Cool the reaction, add acetic acid and evaporate to an oil. Dissolve the oil in methanol, add to an SCX column, wash the column with methanol and elute the product with 2 N ammonia/methanol. Evaporate the solvent to yield the title compound that has a retention time of 3.2 minutes and a mass of 495 (M+1) on LC/MS.

Preparation 11

6-Methoxy-naphthalen-1-yl)-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methanone-2-boronic acid

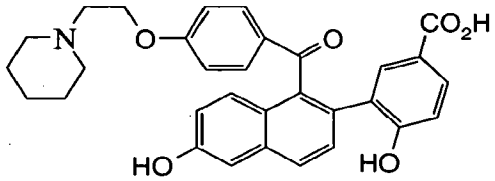


Dissolve trifluoromethanesulfonic acid 6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-benzoyl]-naphthalen-2-yl ester (2.0 gm., 3.72 mmoles) in 125 ml methanol and heat to 55

degrees. To this add tricyclohexylphosphine (208 mg., 0.74 mmoles) followed by palladium II acetate (84 mg., 0.37 mmoles), bis(neopentyl glycolato)diboron (2.5 gm., 11.1 mmoles) and cesium fluoride (1.7 gm., 11.2 mmoles). Stir the reaction at 55 degrees for 4 hours. Cool the reaction, filter, and concentrate the filtrate to 60 ml and purify on an SCX column eluting the product with 2 N ammonia/methanol. Evaporate the solvent, then triturate with ether to give 1.1 grams (69%) of the title compound.

Preparation 12

4-Hydroxy-3-{6-hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-benzoyl]-naphthalen-2-yl}-benzoic acid



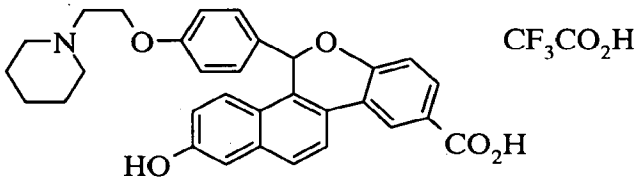
Dissolve 6-methoxy-naphthalen-1-yl)-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methanone-2-boronic acid (433 mg., 1.0 mmoles) and 3-iodo-4-methoxybenzoic acid (556 mg., 2.0 mmoles) in 8 ml of ethanol and add a slurry of 500 mg. of 10% palladium on carbon in 3 ml ethanol followed by 840 mg of sodium carbonate. Flush the vial with nitrogen and seal. Heat the mixture at 72 degrees for 24 hours. Cool, filter, wash the solid with ethanol and discard the solid. Purifty the filtrate on an SCX column, washing with methanol and eluting the product with 2N ammonia/methanol. Evaporate the solvent and purify on a silica column, eluting the impurities with a 0-10% methanol/methylene chloride gradient, then eluting the product with 20% methanol/methylene chloride to give 56 mg, 10%, of 3-methoxy-4-{6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-benzoyl]-naphthalen-2-yl}-benzoic acid.

Convert 3-methoxy-4-{6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-benzoyl]-naphthalen-2-yl}-benzoic acid (56 mg) to the HCl salt and dissolve in methylene chloride. Chill the solution in ice and add excess boron tribromide in portions. Stir at 0 degrees for 1 hour, then at room temperature for 1 hour. Add a few drops of boron tribromide and stir for another ½ hour. Quench the mixture with saturated sodium bicarbonate and wash the water layer with a solvent composed of a 3/1 mixture of chloroform/isopropanol. Adjust

the pH of the water layer to 7 and extract with the organic solvent. Combine the organic layers, dry over 3a molecular sieves and evaporate to a solid. Purify on an SCX column, eluting with 2N ammonia/methanol to give 16 mg (30%) of the title compound.

Example 29

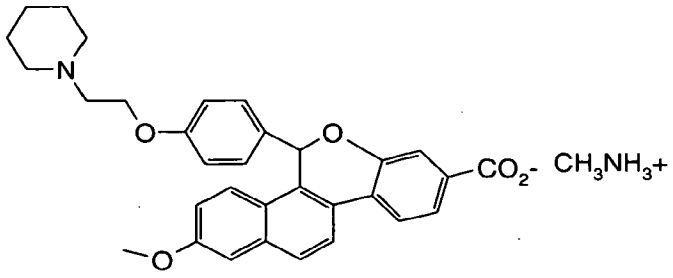
2-Hydroxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-9-carboxylic acid trifluoroacetate



Dissolve 4-hydroxy-3-{6-hydroxy-1-[4-(2-piperidin-1-yl-ethoxy)-benzoyl]-naphthalen-2-yl}-benzoic acid (16 mg.) in 10 ml methylene chloride and add 1.0 ml of trifluoroacetic acid followed by 1.0 ml of triethylsilane. Stir for 1 hour and quench with sodium bicarbonate solution. Extract the water with a 3/1 mixture of chloroform/isopropanol, adjust the water layer to a pH of 7 and extract again. Combine the organic layers, dry over 3A sieves, evaporate and purify by reverse phase HPLC using trifluoroacetic acid in the chromatography solvent to give 7.8 mg (50%) of the title compound. Parent ion of 495 on MS.

Example 30

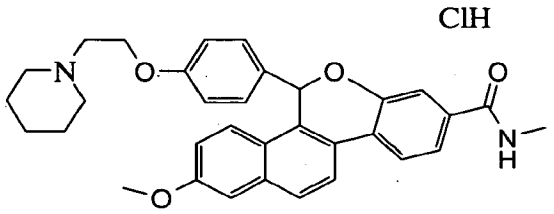
2-Methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-8-carboxylic acid methylamine salt



Dissolve 2-methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-8-carboxylic acid methyl ester (69 mg.) in ethanol and add 1.0 ml of 1 N sodium hydroxide. Warm until all is in solution and let stand overnight. Neutralize with 1 N HCl and add to an SCX column. Elute the product with 2 N methylamine/methanol. Evaporate to dryness, which yields a product with the correct mass. Take the material on to the next step without further purification.

Example 31

2-Methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-8-carboxylic acid methylamide hydrochloride



Dissolve 2-methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-8-carboxylic acid methylamine salt in methylene chloride and add a large excess of oxalyl chloride with stirring. Stir the reaction for 1 hour, and evaporate to dryness. Add methylene chloride and methylamine in THF solution and stir one hour. Add the mixture to an SCX column, wash with methanol and elute the product with 2N ammonia/methanol. The title compound has a retention time of 4.6 minutes and a mass of 523 (M+1) on LC/MS. The compound is converted to the HCl salt and lyophilized giving 60 mg. of product.

Example 32

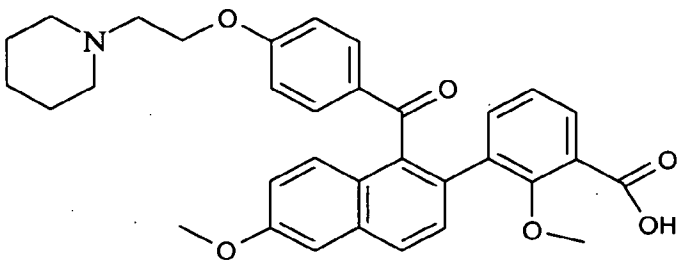
2-Hydroxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-8-carboxylic acid methylamide hydrochloride

Dissolve 2-methoxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-8-carboxylic acid methylamide (56 mg) in 10 ml DMF and add a large excess of sodium t-butylthiolate. Seal the vial and heat at 110 degrees for 48 hours. Cool the mixture, add acetic acid and evaporate to ½ the original volume. Add methanol and run through an

SCX column washing with methanol and eluting the product with 2N ammonia/methanol. Evaporate and purify on a small silica column eluting with 5% methanol/methylene chloride to give 15 mg (30%) of the free base of the title compound which has a retention time of 3.6 minutes and a mass of 509 (M+1) on LC/MS. Convert to the HCl salt and lyophilize.

Preparation 13

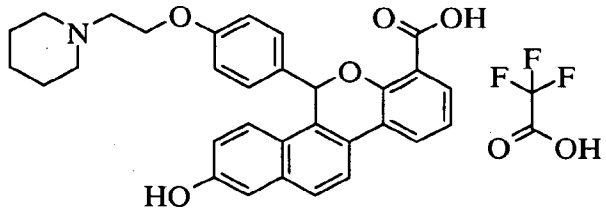
(2-Methoxy-3-{6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-benzoyl]-naphthalen-2-yl}-phenyl)-acetic acid



Place 6-methoxy-naphthalen-1-yl)-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methanone-2-boronic acid (403.0 mg, 0.930 mmol), 2-methoxy-3-bromobenzoic acid (444.8 mg, 1.93 mmol), sodium carbonate (791.3 mg, 7.47 mmol), and 10% Pd/C (~100 mg) in absolute ethanol (20 mL). Place under nitrogen and reflux for 16 hours. Pass reaction through filtering agent and remove solvent. Take up residue in methanol and pass onto SCX resin. Wash resin with methanol and elute product with 2M ammonia in methanol. Remove the solvent and take up the material in 25% isopropanol/chloroform and wash with 1.0M HCl. Separate organic and extract aqueous with 25% isopropanol/chloroform (3x). Dry the combined organics with sodium sulfate and remove solvent. Separate by flash chromatography on silica gel (5-10% methanol/dichloromethane with 1% acetic acid). Scrape the resulting material in toluene and collect by filtration. Wash solid with ether and hexanes. Air dry to give 124.8 mg (24.9%) of the title compound.

Example 33

2-Hydroxy-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5H-6-oxa-chrysene-7-carboxylic acid trifluoroacetate



Dissolve (2-methoxy-3-{6-methoxy-1-[4-(2-piperidin-1-yl-ethoxy)-benzoyl]-naphthalen-2-yl}-phenyl)-acetic acid (124.8 mg, 0.231 mmol) and sodium t-butylthiolate (500.0 mg, 4.46 mmol) in dimethylformamide (20 mL). Place the resulting solution under nitrogen and heat to reflux for one half hour. Cool to room temperature, acidify to pH=2 with 1.0M HCl, and pass onto SCX resin. Wash resin with methanol and 2M ammonia in methanol. Collect all washes and remove solvent. Separate major product by HPLC and dissolve in dichloromethane (20 mL). Add trifluoroacetic acid (2.0 mL) and triethyl silane (2.0 mL). Stir at room temperature for one hour. Wash reaction with brine (50 mL) and separate the organic layer. Extract the aqueous portion with 25% isopropanol/chloroform (3 x 50 mL). Dry the combined organics with sodium sulfate and remove the solvent. Dissolve the residue in methanol and pass onto SCX resin. Wash the resin with methanol and elute the product with 2M ammonia in methanol. Isolate the title compound by HPLC and lyophilize to give 9.2 mg of the title compound: LCMS (8 min): 3.38 min, m/z = 496 (M+1).

Formulation

Because the free base form of a compound of formula I contains a basic moiety (*i.e.*, amino), said compound may be formulated as a pharmaceutical salt, *e.g.*, as the hydrochloride salt or as a salt described in "Handbook of Pharmaceutical Salts: Properties, Selection and Use", Weinheim, New York: VHCA; Wiley-VCH, 2002.

The present pharmaceutical compositions are prepared by known procedures using well-known and readily available ingredients. In making the formulations of the present invention, the active ingredient (formula I compound) will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a

capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semisolid or liquid material which acts as a vehicle, excipient or medium for the active ingredient.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents.

Biological Assays

Estrogen Receptor Binding Assay: Representative compounds of the present invention are screened for binding affinity to both estrogen receptor types (ERα and ERβ). This competition binding assay measures the compound's ability to displace ^{3}H-estradiol and generates IC_{50} and K_i values for both receptor types.

This competition binding assay is run in a buffer containing 50mM Hepes, pH 7.5, 1.5mM EDTA, 150mM NaCl, 10% glycerol, 1mg/mL ovalbumin and 5mM DTT, using 0.025 μCi per well ^{3}H-Estradiol(NEN #NET517 at 118 Ci/mmol, 1 mCi/mL), 10 ng/well ERAlpha or ERbeta receptor (PanVera). A compound of the present invention is added at 10 different concentrations. Non-specific binding is determined in the presence of 1μM of 17-B Estradiol. The binding reaction (140 μl) is incubated for 4 hours at room temperature, then 70 μl of cold DCC buffer is added to each reaction (DCC buffer contains per 50 mL of assay buffer, 750 mg of charcoal (Sigma) and 250 mg of dextran (Pharmacia)). Plates are mixed 8 minutes on an orbital shaker at 4°C. Plates are then centrifuged at 3,000 rpm at 4°C for 10 minutes. An aliquot of 120 μl of the mix is transferred to another 96-well, white flat bottom plate (Costar) and 175 μl of Wallac Optiphase "Hisafe 3" scintillation fluid is added to each well. Plates are sealed and shaken vigorously on an orbital shaker. After an incubation of 2.5 hours, the plates are read in a Wallac Microbeta counter. The data is used to calculate an IC_{50} and % Inhibition at 10μM. The K_d for ^{3}H-Estradiol is determined by saturation binding to ER

alpha and ER beta receptors. The IC_{50} values for test compounds are converted to K_i using Cheng-Prusoff equation and the K_d determined by saturation binding assay.

Ishikawa Cell Proliferation Assay: This assay measures cell proliferation (using an alkaline phosphatase readout) in both an agonist mode in the presence of a compound of the present invention alone, and in an antagonist mode in which the ability of a compound of the present invention to block estradiol stimulation of growth is measured.

Ishikawa human endometrial tumor cells are maintained in MEM (minimum essential medium, with Earle's salts and L-Glutamine, Gibco BRL, Gaithersburg, MD), supplemented with 10% fetal bovine serum (FBS) (V/V), (Gibco BRL). One day prior to assay, growth media is changed to assay medium, DMEM/F-12 (3:1) (Dulbecco's Modified Eagle Medium: Nutrient Mixture F-12, 3:1 Mixture, phenol red-free, Gibco BRL) supplemented with 5% dextran coated charcoal stripped fetal bovine serum (DCC-FBS) (Hyclone, Logen, UT), L-Glutamine (2mM), MEM sodium pyruvate (1 mM), HEPES (N-[2-hydroxyethyl]piperazine-N' – [2-ethanesulfonic acid] 2 mM) all from Gibco BRL). After an overnight incubation, Ishikawa cells are rinsed with Dulbecco's Phosphate Buffered Saline (1X) (D-PBS) without Ca^{+2} and Mg^{+2} (Gibco BRL), and trypsinized by a 3 minute incubation with 0.25% Trypsin/EDTA, phenol red-free (Gibco BRL). Cells are resuspended in assay medium and adjusted to 250,000 cells/mL. Approximately 25,000 cells in a 100ul media are added to flat-bottom 96 wells microculture plates (Costar 3596) and incubated at 37°C in a 5% CO_2 humidified incubator for 24 hours. The next day, serial dilutions of compounds are prepared in assay medium (at 6 times the final concentration in the assay). The assay is run in dual mode, agonist and antagonist modes.

For the agonist mode, plates receive 25 µl/well of assay medium followed by 25 µl/well of a diluted compound of the present invention (at 6x the final concentrations). For the antagonist mode, plates receive 25 µl/well of 6 nM E_2 (β-Estradiol, Sigma, St. Louis, MO) followed by 25 µl/well of a diluted compound of the present invention (at 6x the final concentrations). After an additional 48-hour incubation at 37°C in a 5% CO_2 humidified incubator, media is aspirated from wells and 100 µl fresh assay medium is added to each microculture. Serial dilutions of compounds are prepared and added to the cells as described above. After an additional 72 hour incubation at 37°C in a 5% CO_2

humidified incubator, the assay is quenched by removing media and rinsing plates twice in Dulbecco's Phosphate Buffered Saline (1X) (D-PBS) (Gibco BRL). The plates are dried for 5 minutes and frozen at -70°C for at least 1 hour. The plates are then removed from the freezer and allowed to thaw at room temperature. To each well, 100 µl of 1-Step™ PNPP (Pierce Chemical Company, Rockford, IL) is added. After a 20-minute incubation, plates are read on a spectophotometer at 405nm.

The data is fitted to a linear interpolation to derive EC_{50} (for agonist mode) or IC_{50} (for antagonist mode) values. For the antagonist mode, a % efficacy for each compound is calculated versus E2 (1nM) alone. For the agonist mode, a % efficacy for each compound is calculated versus the response to tamoxifen.

In the agonist mode, the compounds of Examples 1, 2, 3, 5, 6, 8, 11 and 12 were tested and were found to be less stimulatory than tamoxifen. For example, the compound of Example 8 had a relative % efficacy of 15%. In the antagonist mode, these same compounds inhibited greater than at least 80% of the 1nM estradiol response. For example, the compound of Example 8 had an IC_{50} of 9 nM and a % efficacy of 95%.

MCF-7 Proliferation Assay: The MCF-7 cell line was derived from a human breast adenocarcinoma and is used as an indicator of potential antiproliferative activity in breast epithelium.

MCF-7 breast adenocarcinoma cells (ATCC HTB 22) are maintained in MEM (minimal essential medium, phenol red-free, Gibco BRL) supplemented with 10% fetal bovine serum (FBS) (V/V), L-glutamine (2 mM), sodium pyruvate (1 mM), HEPES ((N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]10 mM}, non-essential amino acids(0.1mM)and Penicillin Streptomycin(1X). Seven days prior to assay, MCF-7 cells are switched to assay media which is the same as maintenance medium except supplemented with 10% dextran-coated charcoal-stripped fetal bovine serum (DCC-FBS) assay medium in place of 10% FBS. MCF-7 cells are removed from flasks using 10X Trypsin EDTA (phenol red free, Gibco BRL) and diluted to 1X in (Ca++/Mg++ free HBSS (phenol red-free). Cells are adjusted to 80,000 cells/mL in assay medium. Approximately 8,000 cells (100 µl) are added to each well in 96 well Cytostar T

scintillation plates (Amersham) and incubated at 37°C in a 5% CO_2 humidified incubator for 24 hours to allow cell adherence and equilibration after transfer.

Serial dilutions of a compound of the present invention are prepared in assay medium at 4x the final desired concentration). A 50 µl aliquot of test compound dilutions (at 4x the final assay concentration) is transferred to duplicate wells followed by 50 µl assay medium for the agonist mode or 50 µl of 40pM of E2 for the antagonist mode to a final volume of 200 µl. For each of the agonist plates, a basal level (media) and a maximum stimulated level (with 1µM E2) is determined. For each of the antagonist plates, a basal level (media) and an E2 (10pM) alone control is determined. After an additional 48 hours at 37°C in a 5% CO_2 humidified incubator, 20µl of assay medium containing 0.01 µCi of ^{14}C-thymidine (52 mCi/mmol, 50 µCi/µl, Amersham) is added to each well. The plates are incubated overnight in the same incubator and then counted on the Wallac Microbeta counter. The data is averaged to calculate an IC_{50} and % inhibition @ 1µM for the antagonist mode. For the agonist mode, an EC_{50} and percent of maximum E2 stimulation and concentration of maximum stimulation is calculated.

3-Day Rat Uterus Antagonist Assay: This model for uterine antagonism utilizes immature (3 week old) female rats that are highly sensitive to estrogenic stimulation of the uterus given that their circulating estrogen levels are prepubertal. The uteri from immature rats are fully responsive to exogenous estrogen, yet are quiescent in the absence of exogenous estrogen. Administration of exogenous estrogen to immature rats produces a reliable elevation of uterine weight, which can be used to study uterine antagonist effects. The rats are treated with both estradiol and 4 different concentrations of a compound of the present invention for 3 days and then uterine wet weights are measured.

Nineteen to twenty-one day old (or 45-50g) female rats are orally treated with E2 (0.1 mg/kg, a maximal stimulatory estrogenic stimulus for reliably increasing uterine weight) and 10, 1.0, 0.1 and 0.01mg/kg test compound for 3 days, 6 rats per group. Test compounds are dissolved in 20% β-hydroxycyclodextrin and administered by oral gavage in a volume of 0.2 mL daily (15 min. prior to the ethynyl estradiol gavage). A vehicle control, E2 alone and E2 + raloxifene are also done as controls. The animals are fasted overnight following the final dose. On the following morning, the animals are weighed,

then euthanized (by carbon dioxide asphyxiation) and the uteri rapidly collected (via a mid-line ventral incision) and weighed.

Uterine weight/body weight ratios (UWR) are calculated for each animal. The percent inhibition of the estrogen-induced response is then calculated by the following formula: percent inhibition = 100 x ($UWR_{estrogen}$ - $UWR_{test\ compound}$/$UWR_{estrogen}$ - $UWR_{control}$). ED_{50} values are derived from a semi-log regression analysis of the linear aspect of the dose response curve. Both the UWR data and the percent inhibition data were statistically analyzed by one way analysis of variance (ANOVA) with post-hoc testing by Fisher's PLSD when indicated by a $p \leq 0.05$. Statistical analyses are performed using the Statview® 4.0 software package.

The compounds of Examples 5, 8 and 11 were tested in the above assay and were found to inhibit the estrogen-induced response when administered at 1.0 mg/kg. For example, the compound of Example 11 had an ED_{50} of 0.3 mpk and a % antagonism of 79%.

4-Day OVX Rat Uterine Agonist Assay: In order to assure that a test compound does not have any partial uterine agonist activity, compounds are administered to mature, ovariectomized rats.

Seventy-five day old rats are ovariectomized and treatment is started 14 days later when circulating estradiol levels have reached minimal levels. After 4 days of treatment with 3 doses of a compound of the present invention, (6 rats per group) body weight, uterine wet weight and uterine eosinophil peroxidase (EPO) activity are measured. Cholesterol levels are also measured to compare relative ability to lower cholesterol with other SERMs. If there is any question of uterine stimulation, histological examination will determine epithelial cell height.

The compound of Example 5 was tested in the above assay and did not cause any dose-related statistically significant increase in EPO activity.

10-Day Rat Hormone (Ovarian Stimulation) Screen: An initial, first screen for ovarian toxicity is conducted using a 10-day rat hormone study to measure estradiol and luteinizing hormone levels after compound administration. This screen is conducted by administering compound by oral gavage for 10 days to mature (9-10 week old) F344

female rats. Trunk blood is collected by rapid decapitation for evaluation of LH and estradiol levels approximately 2 hours after the 10th dose. Serum, obtained by centrifugation, is removed and stored frozen below -60°C until assayed. Serum levels of LH and estradiol are measured using radioimmunoassay (RIA) methods.

Rat LH primary antibody and reference preparations (rat LH:RP-3) were obtained from Dr. A. F. Parlow, Director, Pituitary Hormones and Antisera Center, Harbor-UCLA Medical Center, Torrance, CA. The LH assay upper limits of detection were 30 ng/mL and the lower limits of detection were 0.1 ng/mL for the 100 µl samples.

E2 Clinical Assays. DiaSorin s.r.l., Saluggia (Vercelli), Italy. The upper limit of detection was 1000 pg/mL and the lower limit of detection was 5 pg/mL. The compound of Example 5 was tested in the above assay and did not significantly elevate circulating estradiol or LH levels.

35-Day Ovary-Intact Rat Bone Assay: While previous SERMs, including raloxifene have shown efficacy in preventing bone loss in OVX rats, the possibility of interference with estrogen-regulated turnover in ovary-intact rats needs to be addressed.

This assay is done in mature rats with concentrations based on the demonstrated efficacy in the 3-day assay. Generally, at least three concentrations are chosen based on multiples of the ED_{50} generated therein. These multiples are generally 1x, 10x and 30x the ED_{50}. A compound of the present invention is administered to an OVX rat for 35 days and is compared to control, ovariectomized, and/or GnRH-administered rats. Femurs, tibiae, uteri, ovaries and serum are taken for further analyses. DEXA (Dual Energy X-ray Absorptivity), CT (Computed Tomography) and histologic analysis are done on the long bones to assess any changes. CT scans of the distal femur are done to calculate BMD (bone mineral density), cross sectional area and BMC (bone mineral content). Bone strength measurements (load to failure) may also be done to determine consequences of any bone mass or material changes. Uterine and ovarian histology are examined to confirm long term dosing effects of uterine efficacy and potential ovarian stimulation. The serum is analyzed for LH and E2 levels as a possible indicator of ovarian effects.

Utilities

The diseases, disorders or conditions for which a compound of formula I is useful in treating include, but are not limited to, (1) uterine cancer; (2) endometriosis; (3) uterine leiomyoma/leiomyomata; (4) post-menopausal osteoporosis, *i.e.*, osteoporosis caused by the loss of bone that results from a lack of endogenous estrogen such as occurs in a woman following cessation of menstration due to natural, surgical, or other processes; and (5) estrogen receptor postive (ER+) breast cancer, particularly the prevention thereof. Treatment of uterine leiomyoma/leiomyomata as described herein, also contemplates the reduction of the occurrence or severity of the associated symptoms such as pain, urinary frequency, and uterine bleeding.

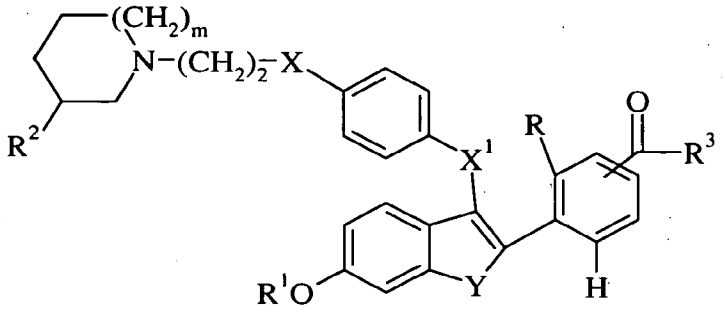
Dose

The specific dose administered is determined by the particular circumstances surrounding each situation. These circumstances include, the route of administration, the prior medical history of the recipient, the pathological condition or symptom being treated, the severity of the condition/symptom being treated, and the age of the recipient. The recipient patient's physician should determine the therapeutic dose administered in light of the relevant circumstances.

Generally, an effective minimum daily dose of a compound of formula I will exceed about 5 mg. Typically, an effective maximum daily dose will not exceed about 350 mg. The exact dose may be determined, in accordance with the standard practice in the medical arts of "dose titrating" the recipient; that is, initially administering a low dose of the compound, and gradually increasing the does until the desired therapeutic effect is observed.

WE CLAIM:

1. A compound of formula I:

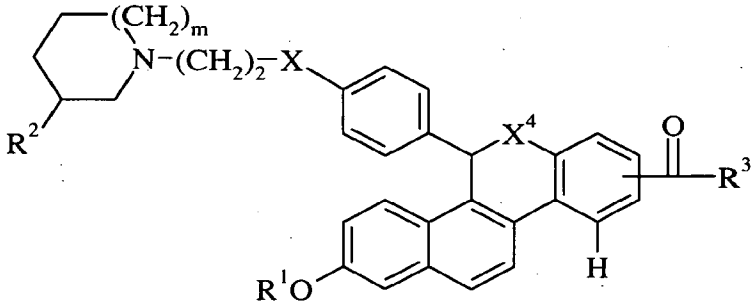


I;

wherein:

m is 0, 1 or 2;

R is H and X^1 is O, CH_2 or CO or R combines with X^1 to form a moiety of the formula:

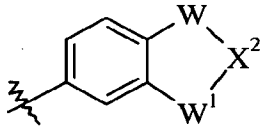


wherein X^4 is O or S;

R^1 is H, SO_2(n-C_4-C_6 alkyl) or COR^4;

R^2 is H or methyl provided that if m is 1 or 2, then R^2 must be H and that if m is 0, then R^2 must be methyl;

R^3 is NR^5R^6 or OR^7 or when R is H, R^3 may combine with the phenyl with which it is attached to form a moiety of the formula:



wherein

W and W^1 are CH_2 or C=O provided that at least one of W or W^1 must be C=O;

X^2 is NR^8 or O;

R^8 is H or C_1-C_6 alkyl;

X is O or NR^9;

Y is S or CH=CH;

R^4 is C_1-C_6 alkyl, C_1-C_6 alkoxy, $NR^{10}R^{11}$, phenoxy, or phenyl optionally substituted with halo;

R^5, R^6, R^7 and R^9 are independently H or C_1-C_6 alkyl; and

R^{10} and R^{11} are independently H, C_1-C_6 alkyl or phenyl; or a pharmaceutical salt thereof.

2. The compound of claim 1 wherein X and X^1 are O and m is 1 or 2.

3. The compound of claim 1 or claim 2 wherein R^1 is H or COR^4 and R^4 is C_1-C_4 alkyl, $NHCH_3$ or phenyl.

4. The compound of any one of claims 1-3 wherein R^1 is H.

5. The compound of any one of claims 1-4 wherein Y is CH=CH.

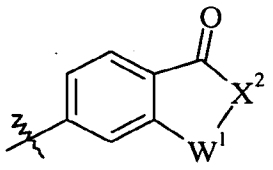
6. The compound of any one of claims 1-5 wherein the COR^3 moiety is at the 3- or 4-position.

7. The compound of any one of claims 1-6 wherein the COR^3 moiety is at the 4-position.

8. The compound of any one of claims 1-7 wherein R^3 is NR^5R^6 and R^5 and R^6 are independently H or C_1-C_4 alkyl.

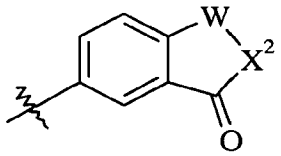
9. The compound of any one of claims 1-7 wherein R^3 is OR^7 and R^7 is H or C_1-C_4 alkyl.

10. The compound of any one of claims 1-7 wherein R is H and R^3 combines with the phenyl with which it is attached to form:



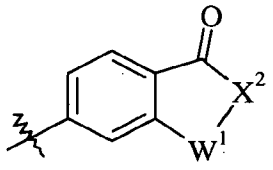
and W^1 is CH_2 and X^2 is NR^8 and R^8 is H.

11. The compound of any one of claims 1-7 wherein R is H and R^3 combines with the phenyl with which it is attached to form:



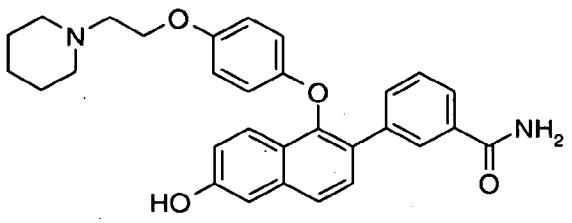
and R^8 is H or C_1-C_4 alkyl.

12. The compound of any one of claims 1-7 wherein R is H and R^3 combines with the phenyl with which it is attached to form:



and R^8 is H or C_1-C_4 alkyl.

13. A compound selected from the group consisting of: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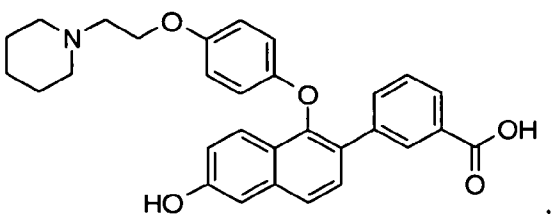
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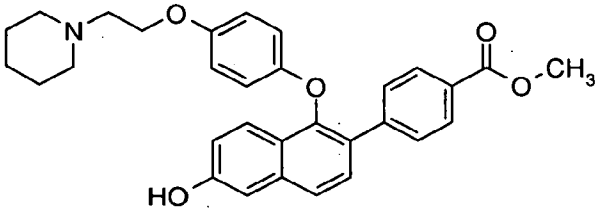
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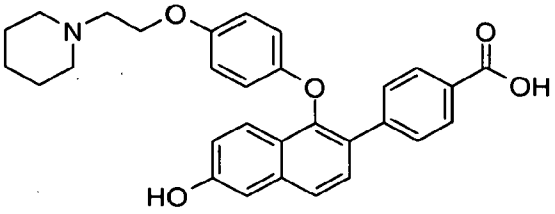
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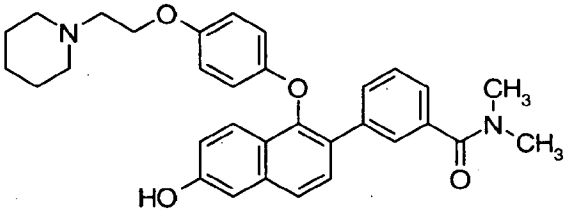
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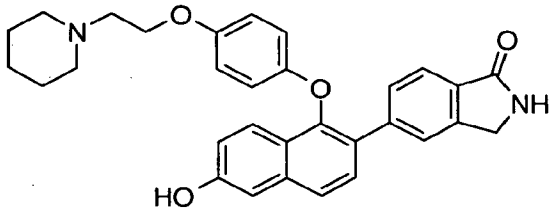
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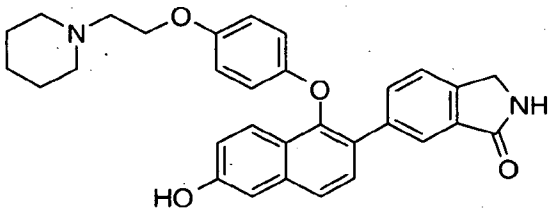
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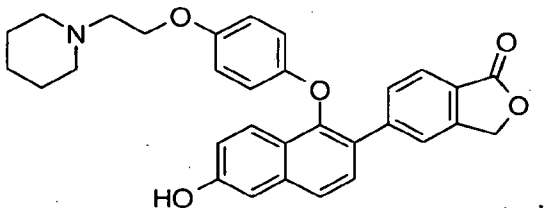
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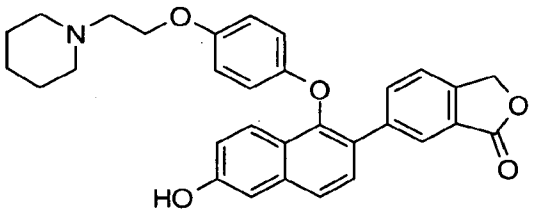
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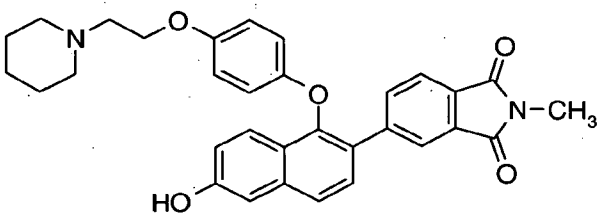
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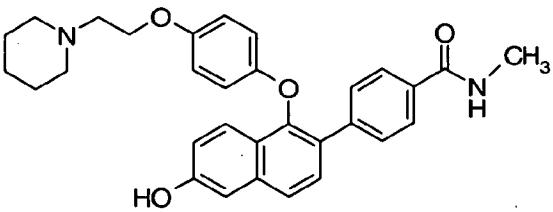
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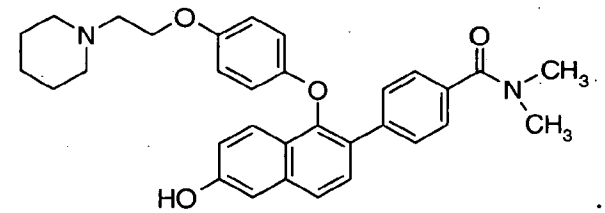
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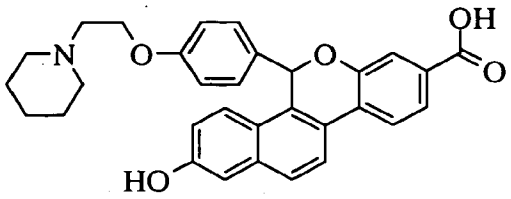
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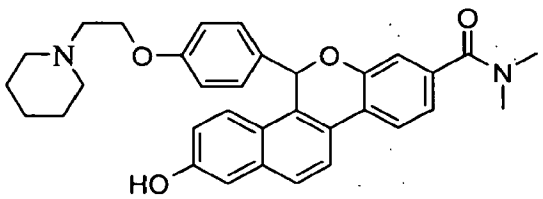
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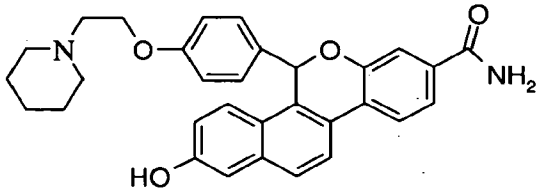
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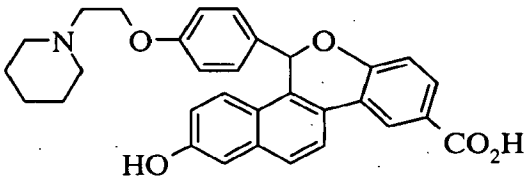
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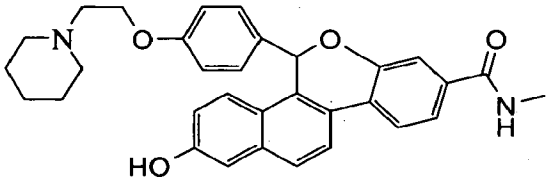
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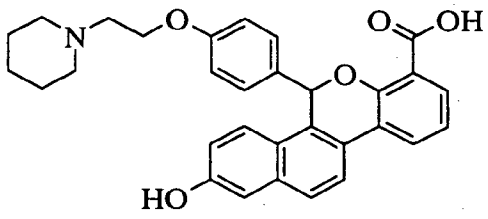

;

or a pharmaceutical salt thereof.

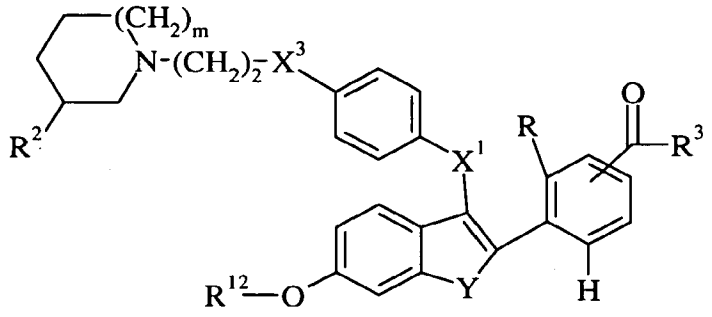
14. The compound of any one of claims 1-13 which is the hydrochloride salt.

15. A method of treating endometriosis comprising administering to a patient in need thereof an effective amount of a compound of any one of claims 1-14.

16. A method of treating uterine leiomyoma comprising administering to a patient in need thereof an effective amount of a compound of any one of claims 1-14.

17. A compound of any one of claims 1-14 for use in treating endometriosis and/or uterine leiomyoma.

18. A compound of formula II:

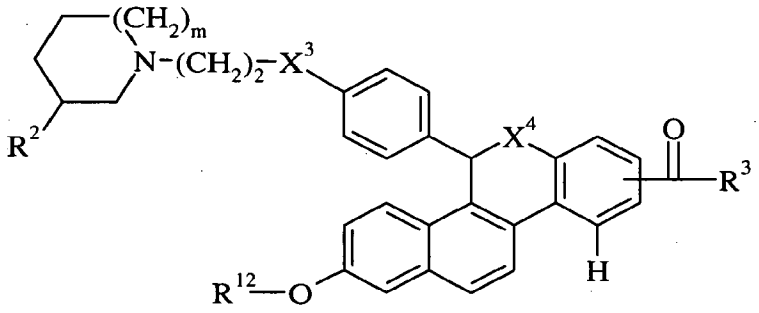


II;

wherein:

m is 0, 1 or 2;

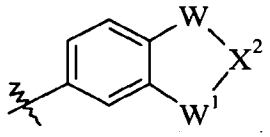
X^1 is O, CH_2 or CO and R is H or R combines with X^1 to form a moiety of the formula:



wherein X^4 is O or S;

R^2 is H or methyl provided that if m is 1 or 2, then R^2 must be H and that if m is 0, then R^2 must be methyl;

R^3 is NR^5R^6 or OR^7 or when R is H, R^3 may combine with the phenyl with which it is attached to form a moiety of the formula:



wherein

W and W^1 are CH_2 or C=O provided that at least one of W or W^1 must be C=O;

X^2 is NR^8 or O;

R^8 is H or C_1-C_6 alkyl;

R^{12} is H, C_1-C_6 alkyl, benzyl, SO_2CH_3, SO_2(n-C_4-C_6 alkyl) or COR^4;

Y is S or CH=CH;

X^3 is O or NR^{13};

R^4 is C_1-C_6 alkyl, C_1-C_6 alkoxy, $NR^{10}R^{11}$, phenoxy, or phenyl optionally substituted with halo;

R^5, R^6 and R^7 are independently H or C_1-C_6 alkyl; and

R^{10} and R^{11} are independently H, C_1-C_6 alkyl or phenyl;

R^{13} is H, C_1-C_6 alkyl or CO_2(C_1-C_6 alkyl); provided that if R^{12} is H, SO_2(n-C_4-C_6 alkyl) or COR^4, then X^3 is NR^{13} and R^{13} is CO_2(C_1-C_6 alkyl); or a salt thereof.

19. The compound of claim 18 wherein X^3 and X^1 are O and m is 1 or 2.

20. The compound of claim 18 or claim 19 wherein R^{12} is SO_2CH_3, benzyl or methyl.

21. The compound of any one of claims 18-20 wherein Y is CH=CH.

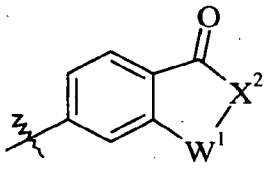
22. The compound of any one of claims 18-21 wherein the COR^3 moiety is at the 3- or 4-position.

23. The compound of any one of claims 18-22 wherein the COR^3 moiety is at the 4-position.

24. The compound of any one of claims 18-23 wherein R^3 is NR^5R^6 and R^5 and R^6 are independently H or C_1-C_4 alkyl.

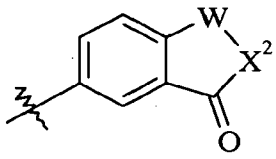
25. The compound of any one of claims 18-23 wherein R^3 is OR^7 and R^7 is H or C_1-C_4 alkyl.

26. The compound of any one of claims 18-23 wherein R is H and R^3 combines with the phenyl with which it is attached to form:



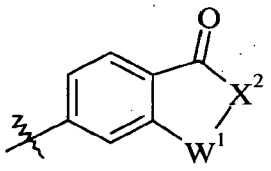
and W^1 is CH_2 and X^2 is NR^8 and R^8 is H.

27. The compound of any one of claims 18-23 wherein R is H and R^3 combines with the phenyl with which it is attached to form:



and R^8 is H or C_1-C_4 alkyl.

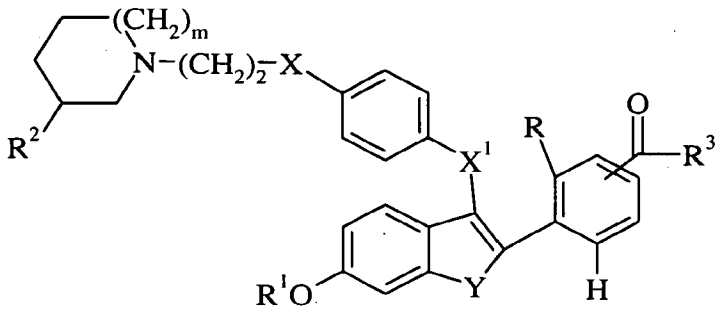
28. The compound of any one of claims 18-23 wherein R is H and R^3 combines with the phenyl with which it is attached to form:



and R^8 is H or C_1-C_4 alkyl.

ABSTRACT

The present invention relates to a selective estrogen receptor modulator of formula I:



I;

or a pharmaceutical salt thereof; useful, *e.g.*, for treating endometriosis and/or uterine leiomyoma/leiomyomata.